HELSINGIN YLIOPISTO

EVALUATION OF AALTOCELL™ AS A FILLER FOR TABLETS COMPRESSED FROM HIGH-SHEAR WET GRANULATED FORMULATIONS

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Abstract

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Abstract:

Microcrystalline cellulose (MCC) is a purified, partially depolymerized cellulose, which is obtained by treating α-cellulose with mineral acids. Ever since the first microcrystalline cellulose was commercialized, different grades of microcrystalline cellulose have widely been used in the manufacture of solid dosage forms, such as tablets. MCC obtained from different sources will exhibit different physico-chemical properties, including moisture content, degree of polymerization, crystallinity, and particle morphology. In wet granulation, microcrystalline cellulose can be used as a filler, binder, and disintegrant. Recently, Aalto University has introduced a novel microcrystalline cellulose obtained from renewable raw materials by an integrated process, which has a short retention time, low energy and chemical consumption. However, very few studies have evaluated the use of AaltoCell™ as an excipient in solid dosage forms.

The objective of this study was to evaluate the filler properties of three grades of AaltoCell™ to prepare paracetamol tablets with 50% (w/w) drug load and compare AaltoCell™ with a commercial microcrystalline cellulose, Vivapur 101. Due to the poor flowability of paracetamol and the experimental microcrystalline celluloses, it is challenging to direct compress tablets from paracetamol and microcrystalline mixtures. Thus, the powder mixtures were granulated by high-shear wet granulation method to improve the flowability. After the granulation, the formulations were characterized for particle size distribution, morphology and powder flow. Carr's index Hausner ratio and angle of repose were calculated to evaluate the flowability of the formulations. In addition, an image-based analysis of powder flow was performed. A rotary tablet press equipped with single punches of 9 mm diameter was used to compress tablets. To evaluate the quality of tablets, European Pharmacopoeia tests of friability, disintegration, uniformity of mass, uniformity of content and dissolution were conducted.

The AaltoCell™ A and Vivapur 101 formulations had the smallest particle size, whereas the AaltoCell™ B had the largest particle size. According to Carr's index and Hausner ratio, the flowability of AaltoCell™ powders and Vivapur 101 varied from poor to very, very poor. After the granulation, the flowability of AaltoCell™ B and AaltoCell™ C were classified as good, while AaltoCell™ A and Vivapur 101 formulations had fair flowability. However, the results were conflicting with the flowability index values obtained in the image-based analysis. According to the results, the AaltoCell™ tablets complied with all criteria of European Pharmacopoeia and were comparable with Vivapur 101 tablets. The average tablet weight deviated ± 3.2% from the target weight. The variations in weight and drug content were small, as indicated by low RSD values. The disintegration time of the AaltoCell™ tablets was between 1-8.5 minutes. In addition, the AaltoCell™ tablets had fast dissolution with 78-84% of paracetamol released within 1 minute.

Overall, AaltoCell™ is a promising excipient for use as a filler in tablets. In further studies, characterizing the powder properties, such as morphology, surface properties and hygroscopicity, would provide a better understanding of the properties of AaltoCell™.

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Tiivistelmä:

Mikrokiteinen selluloosa on eräänlainen puhdistettu, osittain depolymeroitu selluloosa, joka valmistetaan käsittelemällä α-selluloosaa mineraalihapoilla. Siitä lähtien kun ensimmäinen mikrokiteinen selluloosa kaupallistettiin, lukuisia mikrokiteisiä selluloosalaatuja on laajasti käytetty erilaisten kiinteiden lääkevalmisteiden, kuten tablettien, valmistuksessa. Eri lähtöaineista valmistetulla mikrokiteisellä selluloosalla on erilaisia fysikaaliskemiallisia ominaisuuksia, kuten polymeroitumisaste, hygroskooppisuus, partikkelikoko ja morfologia. Märkärakeistuksessa mikrokiteistä selluloosaa voidaan käyttää täyteaineena, sideaineena tai hajotusaineena. Aalto-yliopisto on kehittänyt uudenlaista mikrokiteistä selluloosaa, joka valmistetaan uusiutuvista raaka-aineista integroidulla prosessilla, joka kuluttaa vähemmän energiaa että kemikaaleja. AaltoCell™:in käyttö apuaineena lääkevalmisteissa on kuitenkin vähän tutkittu.

Tämän tutkimuksen tavoitteena oli tutkia kolmen eri AaltoCell™-laadun ominaisuuksia täyteaineena tableteissa, jotka sisältävät 50% parasetamolia (w/w), ja verrata AaltoCell™:iä kaupalliseen mikrokiteiseen selluloosaan, Vivapur 101. Parasetamolin ja tutkittavien mikrokiteisten selluloosien huonon valuvuuden takia jauheseoksia märkärakeistettiin high-shear menetelmällä niiden valuvuuden parantamiseksi. Rakeistuksen jälkeen jauheformulaatioiden hiukkaskokojakaumaa, morfologiaa ja valuvuutta karakterisoitiin. Tabletteja puristettiin rotaatiotablettikoneella käyttäen 9 mm muotteja. Tablettien laatujen arvoimiseksi suoritettiin Euroopan farmakopean mukaiset testit koskien murenevuutta, hajoamista, tablettien painonvaihtelua, annoksen yhdenmukaisuutta ja dissoluutiota.

Tuloksissa selvisi, että AaltoCell™ A- ja Vivapur 101-formulaatioilla oli pienin partikkelikoko ja AaltoCell™ B formulaatiolla oli suurin partikkelikoko. Carr's indeksiarvojen ja Hausnerin suhdelukujen mukaan AaltoCell™ - ja Vivapur 101-jauheiden valuvuusominaisuudet vaihtelivat heikon ja erittäin, erittäin huonon välillä. Märkärakeistuksen jälkeen AaltoCell™ B ja AaltoCell™ C rakeilla oli hyvä valuvuus, kun taas AaltoCell™ A ja Vivapur 101 rakdeiden valuvuus luokiteltiin kohtalaiseksi. Tulokset oli kuitenkin ristiriidassa kuva-analyysiin perustuvalla valuvuustutkimuslaitteella saatujen valuvuusindeksiarvojen kanssa. Tulosten perusteella AaltoCell™ tabletit täyttivät Euroopan farmakopean kriteerit ja olivat ominaisuuksilta verrattavissa Vivapur 101 tablettien kanssa. Tablettien keskimääräien tablettipaino poikkesi ± 3.2% tavoitepainosta (230 mg). Variaatiokertoimien (engl. relative standard deviation, RSD) perusteella tablettien painon ja lääkeainepitoisuuden vaihtelut olivat pieniä. AaltoCell™ -tablettien hajoamisaika oli 1–8.5 minuuttia. Lisäksi parssetamolia vapautui AaltoCell™ -tableteista nopeasti, 78–84% parasetamolista vapautui yhden minuutin sisällä

Tulokset osoittivat, että AaltoCell™ on lupaava apuaine tablettivalmistuksessa. Jatkotutkimuksissa on tärkeä karakterisoida edelleen AaltoCell™:in ominaisuuksia, kuten morfologiaa, partikkelien pinnan karheutta ja hygroskooppisuutta.

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1 INTRODUCTION

Microcrystalline cellulose (MCC) is a purified, partially depolymerized cellulose which is produced by treating α-cellulose, obtained as a pulp from fibrous plant materials, with mineral acids (Galichet 2006). Since MCC was discovered by Battista and Smith in 1955 and first commercialized under the brand name Avicel in 1962, it has emerged as one of the most popular excipients in the manufacture of solid dosage forms, such as tablets. The popularity of MCC comes from its exceptional binding properties, broad particle size distribution, low bulk density, superior flowability, and high dilution potential. In addition, MCC provides other advantages including stability, broad compatibility with active pharmaceutical ingredients (API), little toxic potential, and optimum packing density (Bolhuis and Armstrong 2006, Thoorens et al. 2014). Various grades of MCC are commercially available with different particle sizes, densities, and moisture contents, providing a huge range of applications. It is utilized as a diluent, binder in both direct compression and wet granulation to produce oral solid dosage forms. It has also lubricant and disintegrant properties, which are useful in tablet formulations (Chaerunisaa et al. 2020, Thoorens et al, 2014)

MCC prepared from various cellulose sources by different methods will differ significantly in chemical composition, structure, and physicochemical properties such as water absorption capacity, specific surface area, particle size distribution, and crystallinity, as well as flow and compression behaviour. MCC produced by different manufacturers may have different characteristics due to specific manufacturing processes regarding pulping parameters, subsequent chemical and mechanical processes (Landin et al. 1993).

According to the European Pharmacopoeia (Ph. Eur 11.0 2023), potential critical material attributes of MCC used as a binder, diluent or disintegrant are particle size distribution, particle shape, bulk/tapped/true density, specific surface area, crystallinity, moisture content, and powder flow (Thoorens et al. 2014, Zhao et al. 2020). It is extremely crucial to understand the influences of MCC properties on processing behaviour and final product quality.

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The aim of the literature review part of this work is to provide an overview of the preparation of MCC by different manufacturing processes and present the most important properties of MCC as well as their potential impacts on tableting performance. The application of MCC as a pharmaceutical excipient in wet granulation and the change in their characteristics upon wet processing is also discussed.

In the experimental part of this work, a new MCC grade called AaltoCell^{TM}, which has been introduced by Aalto University and further developed by Nordic Bioproducts Group was studied. The objective of the experimental part was to determine the feasibility of Aaltocell^{TM} as a filler in paracetamol tablets compressed from high-shear wet granulated formulations. Their properties were compared with a commercial MCC, Vivapur 101.

2 LITERATURE REVIEW

2.1 Microcrystalline cellulose and synthesis of microcrystalline cellulose

MCC is defined as a "purified, partially depolymerized cellulose prepared by treating α-cellulose, obtained as a pulp from fibrous plant material, with mineral acids. The degree of polymerization is typically less than 400. Not more than 10% of the material has a particle size of less than 5 μm" (Krawczyk et al. 2009, Vanhatalo 2017). The microfibrils in α-cellulose contain amorphous regions, which are more prone to acid hydrolysis, and crystalline regions, called cellulose crystallites formed by the cellulose chains due to Van der Waals interactions and hydrogen bonding. These crystallites have the same diameter order as the diameter of the cellulose microfibrils (Leppänen et al. 2009, Trache et al. 2016). Figure 1 describes the schematic diagram of MCC separation during acid hydrolysis (Trache et al. 2016). When cellulose reacts with an acid, the acid molecules penetrate the amorphous regions and split the β-1,4 linkages between glucopyranose units of cellulose (Figure 2). The amorphous part is then removed as water-soluble cello-oligosaccharides and glucose, resulting in the reduction of the degree of polymerization (DP) (Krawczyk et al. 2009). The DP decreases rapidly along with the reaction until it reaches a certain level of DP, which is known as the level-off degree of polymerization. As a result of this treatment, the residue contains only tight bundles of crystallite

aggregates, which are the primary MCC particles (Krawczyk et al. 2009, Vanhatalo 2017).

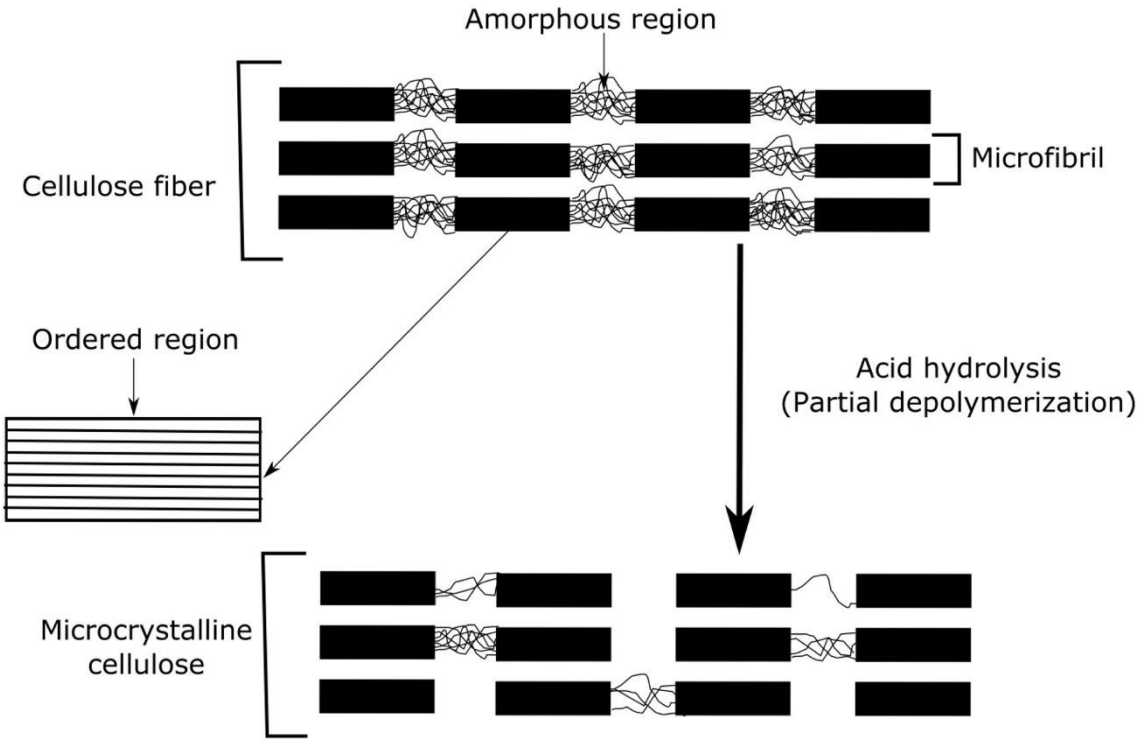


Figure 1. Schematic diagram of MCC preparation during acid hydrolysis (Trache et al. 2016).

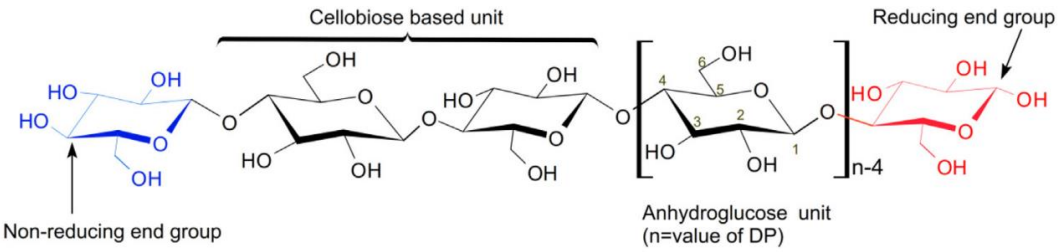


Figure 2. Molecular structure of cellulose showing the numbering of carbon atoms, the reducing end with a hemiacetal, and the non-reducing end with a free hydroxyl at C4 (Trache et al, 2016).

The controlled hydrolysis treatment of cellulose is generally continued by washing, neutralization, filtration, and drying process to produce pure, fine/particle powder of MCC (Figure 3). The neutralized slurry is conventionally spray-dried to the powder form

of MCC and by altering the spray-drying conditions, different MCC grades with desired properties such as moisture content (loss on drying), degree of agglomeration (particle size distribution), binding ability, etc can be achieved (Trache et al. 2016, Chaerunisaa et al. 2020, Thoorens et at. 2014). Other drying techniques have also been studied such as vacuum oven drying followed by grinding into fine powder, freeze-drying, microwaves, and fluidized bed drying (Balaxi et al. 2009, Mohamad et al. 2013, Trache et al. 2014, Trache et al. 2016).

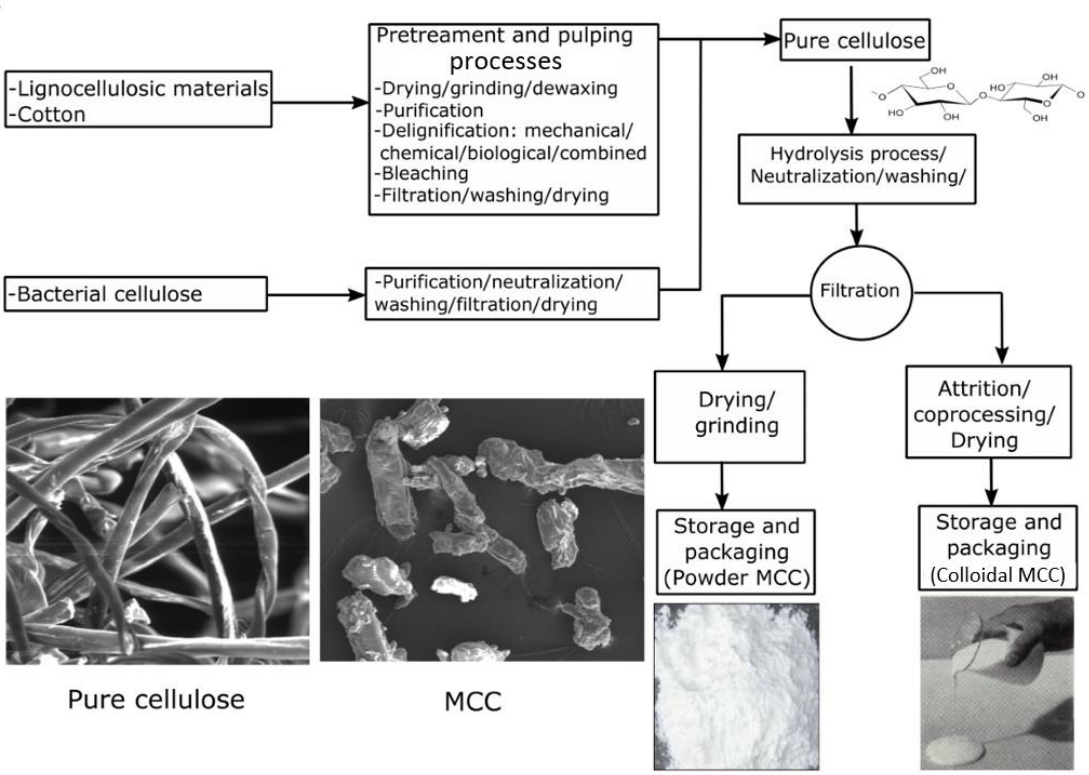


Figure 3. Common steps to produce MCC from raw material to the final product (Trache et al. 2016).

MCC was first commercialized in 1962 under the brand name Avicel® (Trache et al. 2016). Since then, numerous materials have been utilized to produce MCC. The standard raw material of pharmaceutical grade MCC is woods, such as conifers and other softwoods, or hardwoods. Besides wooden sources, attempts have been made to prepare MCC from non-woody lignocellulosic and environmental-friendly materials such as corn residues (Suesat and Suwanruji 2011); cotton waste fabric (Chuayjuljit et al. 2009); sugarcane bagasse, rice straw, and cotton stalk bleached pulps (El-Sakhawy and Hassan

2006); jute (Jahan et al. 2011); sisal fiber (Bhimte and Tayade 2007); hosiery waste (Anand and Chawla 1981). The composition and crystallinity of the MCC are highly dependent not only on the preparation methods, but also on the chemical composition including cellulose proportions, hemicelluloses, and lignin content; and the structural organization (i.e., regions which are relatively more crystalline or amorphous) of the raw material (Landin et al. 1993).

It is possible to synthesize MCC by treating α-cellulose with four main methods: acid and alkaline hydrolysis, enzymatic process, reactive extrusion, steam explosion, or a combined process (Trache et al. 2016, Chaerunisaa et al. 2020). The details of these methods are described in the following sections. Table 1 presents several examples of raw materials and methods used in MCC preparation.

Table 1. Examples of raw materials and methods used in MC preparation.

Raw material	**Hydrolysis agent/method**	**Reference**
Sisal fiber	HCl	Bhimte and Tayade 2007
Jute	H_2SO_4	Jahan et al. 2011
Cotton waste fabric	HCl	Chuayjuljit et al. 2009
Cotton stalks bleached pulps	HCl or H_2SO_4	El-Sakhawy and Hassan 2007
Corn husks and corn cobs	H_2SO_4	Suesat and Suwanruji 2011
Hosiery waste	HCl	Anand and Chawla 1981
Soybean hulls	H_2SO_4	Merci et al. 2015
Soybean husk	HCl	Uesu et al. 2000
Wheat straw	Enzymatic hydrolysis	Monschein et al. 2013
Cotton linters, steam-exploded wood pulp, muslin cloth	Enzymatic hydrolysis	Zabriskie 1984
Steam exploded corn cob, cotton gin waste	HCl, H_2SO_4, enzymatic hydrolysis	Agblevor et al. 2007
Bleached dissolving pulp from mountain spruce	Radiation-enzymatic hydrolysis	Stupinska et al. 2007
Bamboo pulp	HCl – extremely low acid hydrolysis	Zhang et al. 2019
Eucalyptus wood powder	Steam explosion	Vila et al. 2014
Bleached chemical pulp	Steam explosion	Jollez and Chornet 1999

2.1.1 Acid hydrolysis

Acid hydrolysis is the most used method in MCC production due to the shorter reaction time compared to other methods, and it can be applied as a continuous process for producing MCC quickly and efficiently. Moreover, the continuous process requires less acid and the final product contains more fine particles of MCC compared to the batch-type process (Trache et al. 2016). The preparation of MCC based on the hydrolysis of cellulosic material with acids was first reported in several studies by Battista and co-workers. In an experiment conducted in 1950, Battista isolated "crystalline hydrocellulose" using both mild (5.0 M hydrochloric acid at 5^{o}C, 18^{o}C, and 40^{o}C) and drastic (2.5 M and 5.0 M hydrochloric acid at boiling point) conditions of hydrolysis (Battista 1950). It was shown that the percent crystallinity and the levelling-off degree of polymerization were dependent on the hydrolysis conditions during the process. The use of 2.5 M of hydrochloric acid at 105^{o}C for 15 minutes recommended in the study has provided the basis for further research on the influence of materials and processing conditions on preparing MCC (Chuayjuljit et al. 2009, Jahan et al. 2011, Mohamad et al. 2013, Håkansson and Alghren 2005, Leppänen et al. 2009).

Many scientific studies have shown that the reaction conditions (temperature, duration of hydrolysis, acid concentration) and the raw materials have a significant impact on the thermal stability, crystallinity, mechanical, morphological, and physiochemical properties of MCC (Das et al. 2009, El-Sakhaway and Hassan 2007, Trache et al. 2014, Trache et al. 2016). Das et al. prepared MCC particles from cotton slivers using different concentrations (64, 47, 40, 35, 30, and 20%) of sulfuric acid and established a structure-property correlation. They indicated that MCC prepared with lower acid concentrations (20-47%) had higher thermal stability than MCC prepared with 64% sulfuric acid and the increase in acid concentration from 35 to 64% lowered the crystallite size gradually. The authors concluded that the use of lower concentrations of sulfuric acid (35-45%) can yield very fine MCC particles from cotton with a low rate of degradation and good thermal stability (Das et al. 2009). In another study, El-Sakhawy and Hassan produced MCC from agricultural residues using sulfuric acid or hydrochloric acid. They observed that the kind of acid used had no effect on crystallinity, crystallite size, and density of the obtained

MCC. However, the hydrolysis performed by sulfuric acid gave larger-sized MCC particles depending on the starting materials used (El-Sakhawy and Hassan 2007).

Nguyen and Tan (2006) have patented a novel method to produce a new MCC product called texturized MCC from softwood and hardwood. The hemicellulose content in the texturized MCC ranges from about 5% to about 15%, while typical commercial MCC contains about 2-4% hemicellulose. Any mineral acid, such as sulfuric acid, hydrochloric acid and/or nitric acid can be applied as a hydrolysing agent in this process. The acid concentrations were 2-4%, which was milder compared to the original procedure described by Battista et al. (1961). The product had a DP ranging from 150 to 200 and particles of micron and sub-micron size.

Besides traditional hydrolysis methods, Myz et al. 2007 and Kuznetsov et al. 2011 developed advanced procedures using a combination of acetic acid and hydrogen peroxide to carry out the delignification of wood. Myz et al. 2007 established a two-stage process where the catalytic delignification of aspen sawdust was performed by the mixture of acetic acid and hydrogen peroxide in the presence of 2% sulfuric acid; the final delignification was also performed by the mixture of acetic acid and hydrogen peroxide but without catalytic acid. The DP levels for MCC samples from aspen sawdust were 127 to 218 and the crystallinity index was 0.74 compared to commercial MCC samples 0.64-0.80 (Myz et al. 2007). Kuznetsov et al. 2011 reported a one-step catalytic method of preparing MCC from aspen, birch, abies and larch wood in the medium “acetic acid-hydrogen peroxide-water” catalyzed by 2% sulfuric acid. The resultant MCC gained the DP from 128 to 216 and the crystallinity index varied from 0.67 to 0.74 (Kuznetsov et al. 2011).

Acid hydrolysis is a simple and effective method to manufacture MCC from various sources of cellulose. However, this method is not without its disadvantages, including effluent waste issues, especially when using reagents containing chlorine, sulphur and nitrogen, high hydrolysis reaction temperature, equipment corrosion, large amounts of reagents and the formation of undesirable by-products (Nguyen 2006, Trache et al. 2016, Wählström and Suurnäkki 2015).

2.1.2 Alkali hydrolysis

In efforts to overcome the drawbacks caused by using acid hydrolysis, many scientific researchers have utilized alkaline treatment in preparing MCC, which can be achieved at low temperature/pressure (Trusovs 2002). The patent of Trusovs (2002) discloses a method wherein MCC is produced by treating a cellulose source material with an alkaline solution at 20-100^{o}C to induce swelling of the material. Afterward, hydrogen peroxide was added to depolymerize the swollen suspension, hence lowering the viscosity of the suspension. Finally, the alkaline MCC was separated and neutralized by treatment with acid (Trusovs 2002). However, there was a lack of clarity regarding the properties such as DP and crystallinity of the obtained MCC in this study. Nguyen (2006) applied alkali hydrolysis followed by acid treatment to obtain MCC from hardwood and softwood pulps, gaining MCC products with low DP values (95-125) and low hemicellulose contents (3.3-4%). The method was demonstrated to consume less acid and alkali than previous processes and thereby it provides a possibility to produce MCC in a cost-effective and eco-friendly manner.

2.1.3 Enzymatic processes

Besides chemical treatment using acids and alkaline, scientific researchers have employed enzymes as a potential hydrolysis reagent for producing MCC. In comparison to chemical processes, enzymatic hydrolysis generates less undesirable and hazardous waste products; fewer greenhouse gases, and no need for corrosion-resistant equipment or harsh processing conditions (Wahlström and Suurnäkki 2015). Generally, the enzymes used in enzymatic hydrolysis are cellulases and they can be divided into three classes: exoglucanases, which hydrolyse the cellulose chains and cleave off cellobiose units from the ends; endoglucanases, which randomly hydrolyse β-1,4-glucosidic bonds in the cellulose chain and β-glucosidases, which hydrolyze the cellobiose units produced by the glucanases to glucose (Jørgensen et al. 2007, Wahlström et al. 2012). The use of cellulases has been investigated in several MCC manufacturing studies and it was observed that MCC can be produced with different surface characteristics by adjusting enzymatic hydrolysis time (Agblevor et al. 2007, Ibrahim et al. 2013). The enzyme-derived MCC

also exhibited higher DP than the acid-derived MCC, which shows that perhaps the enzymatic hydrolysis provides more accurate control of the DP than the acid hydrolysis (Agblevor et al. 2007). In a study by Zabriskie (1984), cellulase enzymes from various microbial sources were used to prepare MCC from different materials (wood pulp, muslin cloth, exploded wood pulp, and cotton linters), and the tablets compressed from the resultant MCC powder were evaluated for their physical properties. The duration of enzymolysis was found to have a significant impact on the tablet hardness and higher hardness values were obtained by lengthening the hydrolysis time.

Stupinska et al. (2007) employed enzymatic hydrolysis in a two-step radiation-enzymatic depolymerization process to prepare MCC from bleached dissolving pulp. In this process, the pulp was initially depolymerized to a certain level by using an electron beam. Next, the irradiated pulp was subjected to enzymatic hydrolysis to continue the depolymerization. The obtained MCC was proved to be comparable with those applied in the pharmaceutical industry, with the average DP value being 150 and content of crystallinity degree around 64%.

The application of enzymatic hydrolysis in MCC manufacturing can be challenging due to long processing time, high production costs, and lower crystallinity of the MCC products (Hanna et al. 2001). There are also many factors that limit the enzyme performance, including loss of synergism, enzyme denaturation or degradation, and product inhibition. To overcome these limitations, the enzymatic reaction has been combined with other methods, such as acid hydrolysis, to improve the efficacy of the process and extract high purity MCC with a minimum usage of chemical reagents (Trache et al. 2016).

2.1.4 Steam explosion

In the steam explosion process, a non-purified cellulosic material is treated with hot steam (180 to 240^{o}) under pressure (1 to 3.5 MPa) for a short period of time (30s-20 min) in a pressurized reactor, followed by depressurization. The rapid release of steam pressure generates shearing forces that hydrolyse the glycosidic bond and hydrogen bonds between the glucose chains (Bandyopadhyay-Ghosh et al. 2015). The method provides several

attractive features over other technologies: reduced environmental impact, lower capital investment, more potential for energy efficiency, and fewer hazardous process chemicals and conditions (Jacquet et al. 2012). Some authors have successfully employed this process in MCC preparation without the need for conventional acid hydrolysis as a supplement to steam treatment (Ha and Landi 1998, Vila et al. 2014). Nevertheless, the amount of research on the use of steam explosion to produce MCC is still limited compared to other treatments. The reason is probably the high temperature and high pressure required in the process, leading to an increase in energy consumption and thus production cost.

2.1.5 Extrusion

Finally, MCC can be extracted by using the extrusion technique, which has a shorter reaction time than conventional methods. Extrusion processing can provide a continuous reactor environment for a combination of thermo-mechanical and chemical treatment of lignocellulosic materials. Therefore, this approach could be used to extract cellulose from lignocellulosic wastes, employing a procedure with a lower moisture content than other methods (Merci et al. 2015). In the patent of Hanna et al. 2001, MCC was produced by using a reactive extrusion process, wherein the raw material was extruded with a basic aqueous solution to break down the lignocellulosic complex into lignin, hemicellulose, and cellulose. Following extrusion, the lignin and hemicellulose were extracted with a heated basic solution, and the remaining cellulose was hydrolysed by an acid to form microcrystalline cellulose. The quantity of acid in this process was insignificant compared to the conventional methods due to the temperature of the extruder and the pressure created by the die or screw. The acid-cellulose ratio is approximately 1:1 in the reactive extrusion process and from 5:1 to 8:1 in the conventional processes (Hanna et al. 2001). In another study, Merci et al. (2015) described an approach based on the reactive extrusion technique to produce MCC from soybean hulls. However, the utilization of reactive extrusion in MCC manufacturing does not appeal to the scientific community because the number of scientific publications on this subject is not numerous.

2.1.6 AaltoCell™

In 2011, a team led by Aalto University introduced a novel technology, AaltoCell™, which enables efficient and ecological manufacture of MCC from fibrous cellulosic material (Dahl et al. 2011). This novel method enables mass production of MCC by integrating it into a chemical pulp mill, offering cost-efficient production and minimizing global warming potential compared to non-integrated processes. Additionally, the process provides a possibility to produce MCC with controlled lignin contents under favourable conditions including short reaction time, moderate temperature, and low chemical consumption, so that it can be implemented on an industrial pulp mill scale (Vanhatalo 2017, Vanhatalo and Dahl 2014).

According to both patents (Dahl et al. 2011a, Dahl et al. 2011b), the method is based on mild acid hydrolysis at high consistency of at least 8% of dry weight of the fibrous cellulosic material and temperature of at least 140^{o}C or even at 80^{o}C if a part of the manufacturing process is integrated to a kraft pulp mill. The amount of added acid should vary in the range of 0.2 to 10%, preferably from 0. to 5%, and most preferably from 0.5 to 1.5% of dry weight of the material. The MCC product obtained by this method is called AaltoCell™ (Vanhatalo 2017).

2.2 Physical properties of microcrystalline cellulose

2.2.1 Moisture content

MCC is hygroscopic due to the abundance of hydroxyl groups on cellulose chains and relatively large surface to volume ratio of microfibrils (Sun 2008). The moisture content of a typical MCC is usually 3% to 4%, and not more than 5%. The impact of moisture content on the physicochemical properties of MCC, such as compaction properties, tensile strength, and viscoelastic properties, has been extensively investigated in several studies (Doelker et al. 1987, Khan K et al. 1981, Khan F et al. 1988, Sun 2008). In prior research, it was found that the increases in moisture content initially raised the tensile strength and Young's modulus. After reaching a maximum level, the tensile strength and Young's modulus starts to decrease as the moisture content increases (Khan F et al. 1988,

Malamataris et al.1991). This phenomenon can be explained by the combined effect of moisture on the interparticle and intermolecular forces (Malamataris et al. 1991). Later, Amidon and Houghton (1995) reported that as the moisture content increased, the compaction pressure required to generate compacts at a solid fraction of 0.6 fell log-linearly. The authors also observed significant changes in the mechanical properties of MCC at moisture levels above 5% and assumed that it was due to the plasticizing effects of water as the result of a transition from the glassy state to the rubbery state (Amidon and Houghton 1995). Thus, this result supports the moisture content limit of "no more than 5%" set in USP monograph specifications. Sun (2008) found a critical water content ranging from 3.3 to 5% (wt%): below 3.3% water, variations in moisture had no considerable impact on the compaction properties of MCC, while above 5% the bonding strength was reduced with increasing moisture content. The author concluded that when pressure was constant, the tablet tensile strength was optimum at 3.3-5% water levels and decreased when exceeding the limits. This critical range was related to the monolayer coverage and the effects of water on MCC plasticity and interaction strength between bonding surfaces.

Variations in moisture content can also affect flowability. Friction and cohesion are the fundamental forces that influence powder flow (Nokhodchi 2005). Frictional forces act as a tangent at the contact point between particles and oppose the relative motion of the particles. Moisture can act as a lubricant by smoothing out the surface microirregularities and an increase in moisture content will reduce friction due to the lubricating effects. Cohesion in moist powder involves liquid bridges and may also involve solid bridges between particles. Moisture may affect cohesion forces by increasing capillary forces through the creation of liquid bridges (Crouter and Briens, 2014, Dawoodbhai and Rhodes, 1989, Nokhodchi 2005). In the case of MCC, higher shear cell index values were obtained at increasing moisture levels, which indicated a decrease in flowability of MCC (Amidon and Houghton 1995).

It is crucial to control the moisture level of MCC because its high hygroscopicity can affect moisture-sensitive drugs. Changes in moisture content can also profoundly influence different stages during tablet manufacturing and final tablet properties. Shi et al. (2011a) studied the high shear wet granulation of MCC with different initial moisture levels ranging from 0.9% to 10.5% (wt%), while other processing parameters remained

constant. They noticed that larger granules were formed when increasing initial moisture content, which led to enhanced flowability. The most important observation was that even a slight increase in initial moisture from 2.6 to 4.9%, which is within the normal variation of MCC, could result in inferior tableting performance (Shi et al. 2011a). This finding highlights the effect of moisture content on powder flow and tablet properties. From a quality control perspective, it is critical to carefully monitor and control the moisture level in MCC to ensure a robust manufacturing process and high-quality final product.

2.2.2 Particle size

The nominal mean particle size of commonly used MCC grades is in the range of 20-200 µm but there are also many alternative grades available with larger particle sizes (Galichet 2006). Usually, these nominal particle sizes are measured by sieving, laser light diffraction, or volume-based particle size methods, and published standards are based on these results (Gamble et al. 2011). It has been demonstrated that MCC particle populations are composed of individual particles and agglomerates and that the proportion of these individual particles and agglomerates varies between different grades of MCC, contributing to the differences in bulk characteristics (Ek et al. 1994, Gamble et al. 2011).

Multiple studies have pointed out that particle size has only a minor impact on the tabletability of neat MCC, i.e., not lubricated nor blended with other pharmaceutical excipients. In the absence of lubricants, larger MCC particles have similar intrinsic compaction characteristics to smaller MCC particles (Almaya and Aburub 2008, Chaerunisaa et al. 2020, Gamble et al. 2011, Jivraj et al. 2000, Khan and Pilpel 1986, Pesonen and Paronen 1990, Thoorens et al. 2015). Along with moisture content, MCC particle size is often considered as the most important critical material attribute (CMA) for tableting performance (Thoorens et al. 2015). It has been found that lubricant sensitivity is highly dependent on MCC particle size. Coarser MCC particles, characterized by a smaller envelop surface area, demonstrates greater lubricant sensitivity than finer MCC. This phenomenon could be related to the reduction in the surface area accessible to solids (e.g., magnesium stearate), which are unable to penetrate the particle surfaces within the agglomerated particles and thus spread over a smaller surface area,

obstructing bonding formation in the plastically deforming excipient (Gamble et al. 2011). When MCC is combined with other pharmaceutical excipients in a powder formulation, finer MCCs would enhance the tensile strength of directly compressed tablets as well as dry granulated tablets (Kleinebudde and Herting 2007). However, reducing the particle size of MCC will certainly affect its flowability due to increased cohesiveness.

In another study, Kushner et al. (2014) used different grades of MCC (median particle size in the range of 54-228 μm) blending with spray-dried lactose, croscarmellose sodium, magnesium stearate to prepare ibuprofen and theophylline tablets and examined the impact of variability in excipient particle size on the tablet properties. This study confirmed that the variations in excipient particle size influence not only the tablet hardness, friability, and disintegration but also content uniformity. Moreover, particle size distribution may also affect wetting properties, mechanical behaviour, dissolution, and tablet stability (Hlinak et al. 2006, Thoorens et al. 2014).

2.2.3 Particle morphology

Previous studies have shown that MCC morphology exhibits a significant effect on powder flowability as well as other essential tablet properties, such as tensile strength and drug dissolution rate (Li et al. 2022, Obae et al. 1999, Xiu et al. 2020). Obae et al. 1999 employed two types of MCC – PH grade and KG grade to examine the relationship between several structural factors (i.e., morphology of particle, specific surface area) and tablet tensile strength. Rod-shaped (fibrous) particles with a higher L/D ratio (L is the length of particles and D is their width) exhibited larger tensile strength in comparison to round-shaped particles when they were compressed. In a recent study on the influence of MCC morphology on tablet application performance, the fractal dimension was found to correlate well with the tablet hardness. Fractal dimension is a parameter used for quantitatively characterizing particle morphology to express the complexity of particle boundaries and surface roughness (Li et al. 2022). Li et al. (2022) reported that harder tablets were obtained when utilizing MCC powders with high fractal dimensions. This can be explained by increased particle roughness resulting from increasing fractal dimensions and consequently, more contact points were formed between particles,

enhancing interparticle interaction. The study results also revealed that the greater the circularity, i.e., the closer the particle resembled a sphere, the lower the powder compressibility. This in turn led to shorter tablet disintegration time and a higher dissolution rate.

2.2.4 Bulk density

MCC has been known to have relatively low bulk density, with values ranging from 0.32 to 0.45 (Bolhuis and Waard 2011). Hence, it exhibits a high dilution potential on a weight basis, which is highly beneficial for developing high-dose poorly compressible drugs (Habib et al. 1996). A reduced bulk density of MCC also correlates with an increased porosity, which in turn affects the compression behaviour of MCC granules and the tablet forming ability (Johansson and Alderborn 2001). It has been shown that increased intragranular porosity will increase the degree of compression, providing tablets of a closer pore structure and higher tensile strength. The higher roughness of low-density MCC and its irregular shape may also reduce the lubricant sensitivity of MCC granules in terms of their compactability. Different explanations for this observation have been proposed. Firstly, it could be the result of a rupture of lubricant film caused by the deformation or attrition during compression. Secondly, there may be a smaller proportion of the surface of the granules being covered by the lubricant before compression due to rougher surfaces (Johansson and Alderborn 2001). On the other hand, the low bulk density of MCC makes it very cohesive and thus poorly flowable. This limitation of poor flow can be overcome by combining MCC with another filler with good flowability, such as α-lactose monohydrate or dicalcium phosphate dihydrate (Jivraj et al. 2000).

2.2.5 Specific surface area

Particle size, surface roughness, and porosity serve as important factors contributing to the specific surface area. In general, smaller particle size, porous structure, and fine surface protrusions result in higher specific surface area (Osei-Yeboah et al. 2014). The specific surface area and surface roughness of MCC particles may have a beneficial impact on the tableting properties because of extensive hydrogen bonding between large

surface areas, and mechanical interlocking which is contributed by irregularly shaped particles. These features are believed to account for the excellent binding properties of MCC (Nyström et al. 1993, Pesonen and Paronen 1990, Westermarck et al. 1999, Wu et al. 2001a). However, the large surface area of MCC may make it very cohesive, leading to relatively poor flowability.

2.2.6 Crystallinity

MCC has an atypical semi-crystalline structure consisting of crystalline and amorphous regions. Its degree of crystallinity ranges around 55-85%. The broad range of the degree of crystallinity of MCC can be caused by different factors, such as the kinds of pulp used as raw materials, processing conditions, different manufacturing methods and techniques for measuring crystallinity (e.g., X-ray diffraction, infrared spectroscopy, solid-state NMR) (Landin 1993, Rowe et al. 1994, Suzuki and Nakagami 1999).

The crystallinity of MCC can be modified by the grinding process or compression process (Awa et al. 2015). Meanwhile, the hydrolysis factors including temperature, acid concentration, and duration of hydrolysis have been reported to have a negligible effect on the degree of crystallinity, i.e., the regularity of MCC polymer chains is not affected by these factors (Wu et al. 2001). Therefore, the crystallinity of MCC cannot be controlled by altering hydrolysis conditions. Crystallinity appears to be more dependent on pulp source than on processing, which can be explained by the MCC manufacturing approach where the acid preferentially targets the pulp-dependent amorphous regions (Landln et al. 1993, Thoorens et al. 2014).

Several studies have reported the effects of MCC crystallinity on its behaviour during processing. It appears that a reduction in tabletability can be observed only when the crystallinity is significantly decreased. Pesonen and Paronen (1990) reported that there was no correlation between the crystallinity and the strength of tablets when the degree of crystallinity was in the range of 63-68% for Avicel and Emcocel. In another study, Suzuki and Nakagami (1999) were able to decrease MCC crystallinity from 65.5 to 12.1% with pulverization time due to mechanochemical effects and successfully detected the relationship between the degree of crystallinity of MCC and tablet hardness in this wide

range. A decrease in crushing strength was observed as the degree of crystallinity became smaller. Based on the results obtained in this study, the authors proposed that the crystalline region and amorphous region in the MCC structure may be fractured and deformed plastically during compression, respectively. Moreover, the dissolution profiles of tablets were found to be related to the degree of crystallinity. The dissolution rate of acetaminophen decreased when the degree of crystallinity of MCC was reduced from 65.5 to 37.6%, but it increased when the degree of crystallinity varied from 25.8 to 12.1%. It is evident that the degree of crystallinity plays a role in controlling the dissolution rate of tablets containing MCC. Since the dissolution rate did not linearly correlate with the crystallinity of MCC, more research is needed to clarify this observation.

The amount of absorbed water in MCC tablets has been shown to depend on the crystallinity because the disordered amorphous regions of MCC tend to bind water molecules more strongly via hydrogen bonds between the MCC particles and water (Amidon and Houghton 1995, Awa et al. 2015, Nokhodchi 2005, Suzuki and Nakagami 1999). Therefore, a reduction in the crystallinity will result in higher moisture absorbability of MCC powders and consequently affect the pharmaceutical properties of tablets, especially in the case of moisture-sensitive APIs.

2.2.7 Degree of polymerization

The degree of polymerization (DP) expresses the average number of single glucose units ($C_6H_{10}O_5$) in each chain (Chaerunisaa et al. 2020). During the first stage of reaction, the hydrolysis proceeds rapidly and the DP decreases exponentially. The rate of reaction slows down during the second stage, until the DP of the cellulosic residue reaches a so-called “level-off degree of polymerization” (LODP). It is defined as the DP at which no further acid hydrolysis reaction occurs, ranging between 100-300 glucose units. DP values are generally lower than the LODP, and it is more difficult to control DP values greater than the LODP plateau because of their increased sensitivity to hydrolysis factors (Chaerunisaa et al .2020, Thoorens et al. 2014). The LODP value is specific for a particular raw material, typically less than 400, ranging from 180 to 210 for hardwood pulps and from 210 to 250 for softwood pulps. Unlike the degree of crystallinity, the DP of MCC is more sensitive to the hydrolysis factors (temperature, the acid used,

concentration of acid, and time of hydrolysis) and strongly dependent on the raw material (Doelker 1993, Thoorens et al. 2014, Trache et al. 2016).

The DP of MCC has a remarkable influence on the characteristics of MCC. Shlieout et al. (2002) observed a correlation between the DP of MCC and tablet hardness. The investigation of the compactability showed that the crushing strength of MCC tablets decreased as the DP was lowered, but a significant difference was only seen between DP 190 and the other DPs (244 and 299). No obvious differences were found between MCC with DP values of 244 and 290 when the same particle size fraction was compressed, but both showed better tabletability than DP 190. Moreover, the study also suggested that the water absorption of MCC is proportional to its DP. MCCs with a high DP may contain more water than the grades with a low DP, probably due to the higher molecular weight, which adds to the water binding positions (Shlieout et al. 2002). It has also been found that the bulk density and tap density of MCC drop when increasing the DP, leading to improved tablet tensile strength (Liao et al. 2012, Shlieout et al. 2002).

Above the LODP value, MCC tends to have more fibrous cellulose characteristics and therefore a lower bulk density, which would enhance the tableting properties, but at the same time would deteriorate the flowability of MCC powder. Below the LODP, MCC is less fibrous, and it has higher density and poorer tabletability. During the production of MCC, it is critical to strictly control the hydrolysis conditions to conform to the specifications for DP and bulk density (Thoorens et al. 2014).

2.3 Compaction and compression behaviour of microcrystalline cellulose

MCC has been known to possess outstanding compactability and binding properties, which are contributed by its high plasticity, high viscoelasticity (time-dependent behaviour), low brittleness (fragmentation propensity), and particle interlocking (Doelker 1993). When compressed, MCC particles undergo plastic deformation, forming a strong compact due to an extremely large number of clean surfaces brought in contact during this deformation and the strength of the hydrogen bonds formed (Chaerunisaa et al. 2020, Schwartz and Lachman 190). Usually, Heckel plots, force-displacement curves, and creep analysis are utilized to describe the plastic behaviour of MCC (Bolhuis and Waard 2011).

The plastic deformation process is a function of time and therefore, the compressibility of plastically deforming materials is affected by the speed of compaction (Wu et al. 2001b). Brittle excipients, such as dicalcium phosphate dihydrate, are less sensitive to compaction speed due to the rapid fragmentation of particles under compression. Moreover, plastic materials are more susceptible to capping, lamination, and/or strength reduction when increasing the punch speed, especially at the speed of 600 mm/sec. An increase in punch velocity also results in higher yield pressure in the case of plastically deforming materials, whereas brittle materials exhibit no change. The plasticity of MCC is also believed to increase with increasing compression force, accompanied by a reduction in viscoelasticity (Bolhuis and Waard 2011). In addition, as an effect of their high plasticity, MCC is more lubricant sensitive compared to brittle materials (Ruegger and Celik 2000, Thoorens et al. 2014). Lubricated MCC particles will undergo plastic deformation under pressure and will not generate enough fresh surfaces (lubricant-free) to strengthen the bonding of the granules. The use of mixtures containing two or more compression excipients that consolidate by different deformation mechanisms (i.e., by plastic deformation, fragmentation, or intermediate behaviour) can improve the compaction properties of a formulation and eliminate the negative influences of lubricants on tablet strength (Thoorens et al. 2014, Wang et al. 2010).

Ishino et al. (1990) investigated the effect of compression rate on compactability and compressibility of MCC and α-lactose monohydrate, with different particle sizes (100-250 μm) under high-speed compression. The authors found that the tableting speed and particle size distribution did not affect the hardness of tablets containing lactose (brittle material), whereas MCC tablets displayed compression-rate-dependency in the consolidation of larger particle size fractions (180-250 μm). For smaller particle size fractions of MCC (100-150μm), the tableting speed did not remarkably influence the tablet strength. This phenomenon can be explained by the fact that larger particles are more prone to plastic deformation than smaller particles. It was also observed that smaller MCC particles were able to form tablets with higher tensile strength than larger particles, even though the porosity of compacts was the same. This is probably due to the superior packing ability of smaller particles (Ishino et al. 1990).

As mentioned in the previous paragraph (2.2.1 Moisture content), the moisture content of MCC has a remarkable influence on its compactability. Most of the water will be in the porous structure of MCC at its equilibrium moisture content of 5%, and a large amount of this bound moisture is hydrogen-bonded to small bits of cellulose within the particle. When MCC deforms plastically, the moisture within the pores may act as an internal lubricant, allowing slippage and flow within individual microcrystals. At optimum water content, elastic recovery will be hindered as more bonds are formed through hydrogen bridges (Bolhuis and Waard 2011, Thoorens et al. 2014).

2.4 Flow properties of microcrystalline cellulose

Flowability of MCC can vary greatly depending on their grades (Doelker et al. 1995, Gamble et al. 2011, Sun et al. 2010). The original grade of MCC, Avicel PH-101, has an average particle size of 50 µm and is often described as poorly flowable. Its poor flow properties are explained by the more or less long-crawn, matchstick-like form of the particles, the particle size distribution, and the low bulk density. The larger particle size and higher-density MCC grades generally provide better powder flow (Bolhuis and Waard 2011, Chaerunisaa et al. 2020, Thoorens et al. 2014). Doelker et al. (1995) analyzed the flow properties of six MCC grades (Avicel PH-101, Avicel PH-102, Avicel PH-103, Avicel PH-105, Avicel PH-112, Avicel PH-200) and reported their rank order of flow rates as Avicel PH-200 >> Avicel PH-112 = Avicel PH-102 > Avicel PH-103 > Avicel PH-101 > Avicel PH-105 based on the calculated Hausner ratios, with Avicel PH-200 having the best flowability and Avicel PH-105 the poorest flowability. The improved flow properties of Avicel PH-200 are attributed to the presence of larger agglomerates (Figure 4). The recorded percentages of agglomerated particles by volume for PH-101, PH-102, and PH-200 grades were 36-39%, 38-58%, and 50-71%, respectively (Gamble et al. 2011). Even though Avicel PH-200 is regarded as having the best flow among the conventional MCC grades, its flowability can only be described as moderate.

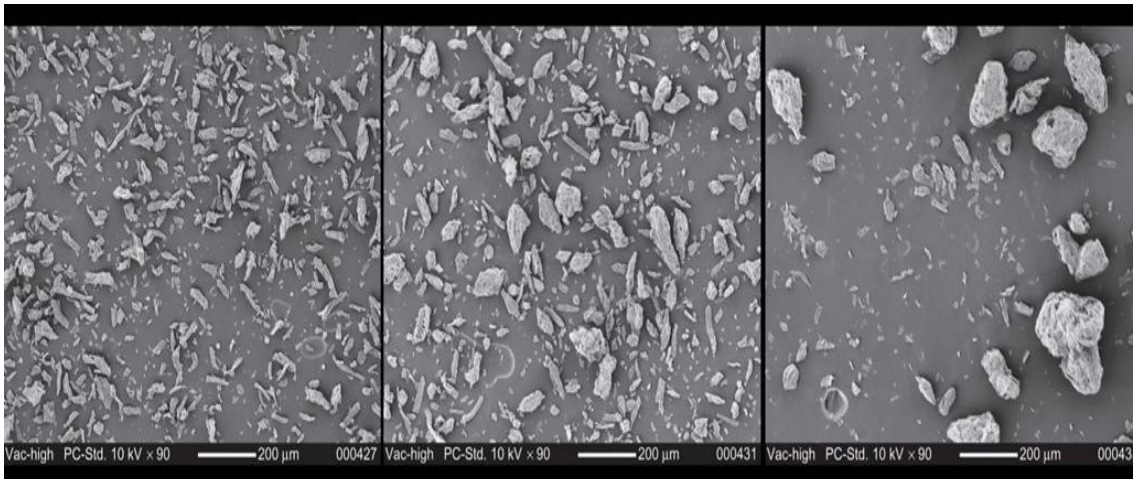
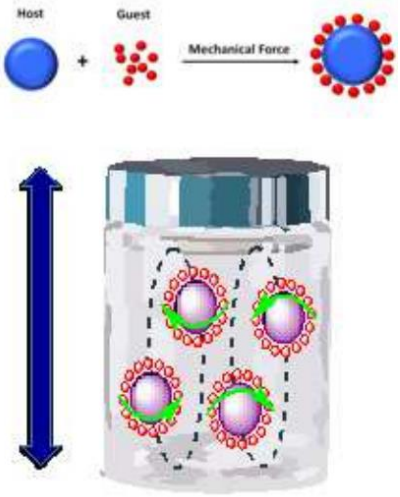


Figure 4. From left to right: SEM image of Avicel PH-101, Avicel PH-102, and Avicel PH-200 at 90x magnification (Gamble et al. 2011).

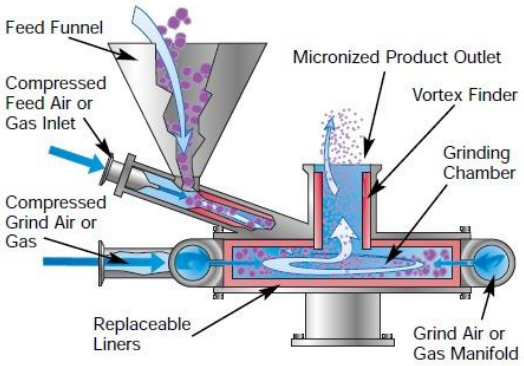
Sun (2010) produced tablets from different Avicel grades (PH-302, PH-102, PH-101, and PH-105) to establish a relationship between powder flow properties and flow behaviour during high-speed tableting. The powders were compressed by a Korsch XL100, 12 stations, and at a press speed of 70 rpm. It was reported that Avicel PH-102 showed minimally acceptable flow properties required for successful high-speed tableting. Later, the batch-to-batch reproducibility of the flow properties of Avicel PH-102 was also proven to be acceptable by shear cell measurements (Shi et al. 2011b). These studies suggested that Avicel PH-102 can be used as a reference material to predict the flowability of a powder during high-speed manufacturing. Any powder having lower flow properties than Avicel PH-102 may pose problems during tableting due to inadequate flow and hence, such powder should be avoided in tablet formulation.

Expected powder flowability can be obtained by selecting MCC grades with a larger proportion of agglomerates, such as Avicel PH-200, or by combining MCC with other free-flowing materials. Moreover, several high-functional MCC grades have been developed to provide improved flowability and better compressibility. For example, Avicel PH-301 has the same particle size as PH-101 (50 µm) but higher density providing better flow rate and tablet weight uniformity; or silicified MCC has excellent compactability, improved blending properties and binding properties (Chaerunisaa et al. 2020). One approach to enhance the flow properties of cohesive and poorly flowable materials is to coat nano-silica onto the surface of the particles (Chen et al. 2018, Chen et

al. 2020, Yang et al. 2005). In a study by Chen et al. 2018a, Avicel PH-105 was dry coated with three different amounts of Aerosil 200 (0.5, 0.7, and 1 wt%) through a one-step process using a high-intensity vibrational mixer, called Resonant Acoustic Mixer (LabRAM). The results showed that even at reduced concentrations of Aerosil 200 (0.5-0.7 wt%), the nano-silica dry-coated Avicel PH-105 exhibited significant improvements in flowability, bulk density, and tablet tensile strength, in comparison to several commercially available MCCs including Prosolv 90, Prosolv HD 90, Prosolv 50, Prosolv 50 LD, Avicel PH-101, and Avicel PH-102. Although the nano-silica-coated Avicel PH-105 suffered from 9-12% loss of compaction, it still outperformed Prosolv grades (Chen et al. 2018). Later, Chen and co-workers (2020) studied three different methods for dry coating fine grade of MCC. They dry-coated milled Avicel PH-102 (~ 30 µm) with 1 wt% hydrophilic silica A200 using LabRAM and a conical mill (Comil), and a pre-blended mixture of Avicel PH-102 and 1 % A200 was milled and coated down to ~ 30 µm by fluid-energy milling (FEM) (Figure 5). The MCCs obtained from all three coating methods achieved higher bulk density and flow function coefficients compared with Avicel PH-102. In addition, it was surprising that all three formulations of ibuprofen tablets containing 17 wt% coated MCC and 60 wt% ibuprofen had higher bulk density, higher or similar flowability, and higher tablet tensile strength in comparison to formulations with silicified MCC, Prosolv 50. However, it should be noted that dry coating with silica could decrease bonding strength, leading to deteriorated compactability (Chen et al. 2018).



A)



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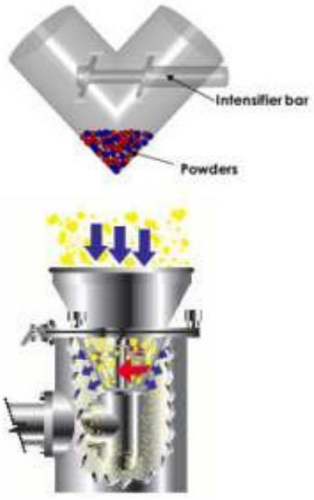


C)

Figure 5. Process schematic for a) LabRAM coating, b) FEM coating, and c) Comil coating (Chen et al. 2020).

2.5 Commercially available microcrystalline cellulose grades

MCC was first commercialized in 1962 under the brand name Avicel® by FMC Corporation and introduced to the pharmaceutical industry as an excipient for direct compression in 1964 (Thoorens et al. 2014, Trache et al. 2016). Nowadays, numerous grades of MCC are commercially available in different particle sizes, densities, and different properties, offering a variety of applications in the pharmaceutical industry. The main characteristics of most commercial MCC grades are achieved by manipulating the drying process to control the particle size distribution and moisture content. Higher bulk density grades of MCC are also available by using different cellulose sources, and finer grades with particle sizes below 50 µm, such as Avicel PH-105 (Figure 6), can be obtained by further milling the spray-dried MCC (Carlin 2008, Thoorens et al. 2014). The properties and utilization of several MCC types are summarized in Table 2. Avicel PH-101 and Avicel PH-102 are the most used MCC grades.

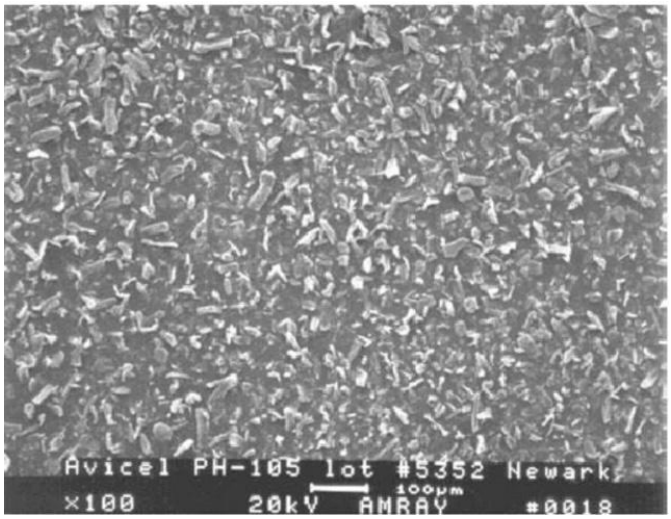


Figure 6. Scanning electron micrograph of Avicel PH-105 (particle size 20 µm) (Carlin 2008).

Table 2. Properties and applications of several commercially available MCC grades (NMT = not more than).

MCC type	Particle size (µm)	Moisture content (%)	Utilization
Avicel PH-101 [(a)]	50	NMT 5.0	A fine grade MCC, most widely used in direct compression, wet granulation, spheronization, and capsule filling process. Final blending is not recommended due to poor flowability (Chaerunisaa et al. 2020, Galichet 2006).
Avicel PH-102 [(a)]	100	NMT 5.0	Coarser grade than PH-101 with improved flowability. It is used as a flow aid, compression aid, filler, and binder in direct compression; as a diluent and disintegrant in wet granulation. Both PH-101 and PH-102 have high carrying capacity, strong hydrogen bonding properties, and good physical stability (Chaerunisaa et al. 2020, Galichet 2006).
Avicel PH-103 [(a)]	50	NMT 3.0	Avicel PH-103 has a lower moisture level, therefore it can be used for moisture-sensitive APIs (Chaerunisaa et al. 2020, Galichet 2006).
Avicel PH-105 [(a)]	20	NMT 5.0	Extra-fine Avicel grade which maximizes tablet strength. This grade can be used for temperature- and pressure-sensitive APIs due to its excellent compactability. PH-105 is used in direct compression, dry granulation, and wet granulation. To further boost compression and flow, PH-105 is mixed with PH-101 and PH-102. It is also recommended for roller compaction (FMC Biopolymer).
Avicel PH-112 [(a)]	100	NMT 1.5	PH-112 is used for moisture-sensitive APIs due to its low moisture content. This grade provides the formulators a possibility to prevent moisture uptake during long-term storage, optimize drug stability and avoid the use of low-humidity facilities.
Avicel PH-113 [(a)]	50	NMT 2.0	PH-113 has the same particle size as PH-101, but lower moisture content. It is used for moisture-sensitive APIs (FMC Biopolymer).
Avicel PH-200 [(a)]	180	NMT 5.0	PH-200 has the largest particle size among Avicel grades. It is used in direct compression and wet granulation. PH-200 can be used to improve flowability

			and content uniformity; to reduce tablet weight variation, tablet friability, and lubricant sensitivity. Other benefits of PH-200 are high dilution potential and anti-adherent properties (FMC Biopolymer).
Avicel PH-301 [(a)]	50	NMT 5.0	PH-301 has the same particle size as PH-101 but higher density and greater flowability. This grade is used for making small tablets. It increases tablet weight uniformity even at high tableting speeds and can be blended with PH-200 or PH-102 SCG to boost compression mix compactability (FMC Biopolymer).
Avicel PH-302 [(a)]	100	NMT 5.0	PH-302 has the same particle size as PH-102 but is denser, providing an increase in batch weight for the same blender volume by 20% compared to PH-102. It is usually used in direct compression but can also be utilized to maximize flow for powder fill in making hard capsules (FMC Biopolymer).
Celex 101 [(b)]	75	NMT 5.0	Celex 101 is used to enhance flow, lubricating and binding properties; and to reduce friability and weight loss in direct compression tableting (International Specialty Products).
Ceolus KG-802 [(c)]	50	NMT 6.0	Ceolus KG-802 has a needle-like particle shape and hence less elastic recovery and more particle-to-particle entanglements, providing higher tablet strength. It is applied in direct compression, wet granulation, and dry granulation. This MCC type is suitable for Orally Disintegrating Tablet (ODT) and Multi Unit Particulate System (MUPS). It reduces tablet friability, facilitates high dosage formulation, and prevents sticking and capping (Asahi Kasei Corporation).
Emcocel 50M [(d)]	65	NMT 5.0	Emcocel 50M is a fine standard MCC grade with superior compactability, recommended for wet granulation, roller compaction, and spheronization (JRS Pharma (a)).
Emcocel 90M [(d)]	130	NMT 5.0	Emcocel 90M has good flow and good compactability. It is suitable for most directly compressive actives (JRS Pharma (a)).
Emcocel HD90 [(d)]	130	NMT 5.0	HD90 has the same particle size as 90M but has higher bulk density and better flowability. It is used especially

			for high-speed tableting and processing high-density actives (JRS Pharma (a)).
Vivapur 101 [(d)]	65	NMT 5.0	Vivapur 101 is a fine, conventional MCC grade for wet granulation, roller compaction, and spheronization. It has very high compactability (JRS Pharma (b)).
Vivapur 102 [(d)]	130	NMT 5.0	Vivapur 102 has a medium particle size, high flowability and high compactability. This grade is suitable for directly compressible actives (JRS Pharma (b)).
Vivapur 12 [(d)]	180	NMT 5.0	Vivapur 12 is a coarse MCC grade, which provides excellent compactability, binding capacity and flowability. It improves content uniformity at low weight variation, even when used with low concentrations of fine actives (JRS Pharma (b)).

Suppliers: [(a)] FMC Biopolymer; [(b)] International Specialty Products; [(c)] Asahi Kasei Corporation; [(d)] JRS Pharma.

Doelker et al. (1987) conducted the most complete comparative evaluation of MCC by studying the tableting and packing characteristics of sixteen MCC products from seven manufacturers. The samples including nine fine powders (type I) and seven coarser powders (type II) were evaluated for moisture content, particle size distribution, density, flow rate, lubricant sensitivity, and compression properties. Great differences in packing and tableting properties and lubricant sensitivity were observed between samples from various manufacturers. These differences were attributed to variations in moisture content, particle size distribution, particle shape, and internal structure caused by varying processing conditions during the manufacture of the MCC. In contrast, lot-to-lot variability was acceptable. Variations may be found among different MCC products, even if they conform to compendial standards (Doelker et al. 1993). For that reason, the substitution of one product for another must be validated (Carlin 2008, Thoorens et al. 2014).

2.6 Application of microcrystalline cellulose in wet granulation

2.6.1 Wet granulation process

The wet granulation method is a process of size enlargement, which is used to minimize the risk of segregation, reduce dustiness and enhance the formulation properties such as flowability, compactability, and density (Wade 2019). In addition, wet granulation also improves the wettability of poorly soluble drugs. During wet granulation, a powder is initially dry blended, followed by the addition of a granulation liquid to facilitate wetting and agglomeration of small particles to form granules. The mass is mixed until reaching the desired endpoint, which could be defined by mixing time, amount of added binder solution, and power or torque reading on the mixing impeller. The wet granules are subsequently dried to eliminate the binder solution and milled to obtain granules of the desired particle size. Finally, the granules could be mixed with a lubricant, as well as a small amount of extra-granular binder and disintegrant to produce the final granule mix that is uniform, exhibits good flow, adequate compaction properties, and tableting properties. The wet granulation process involves three stages: (a) wetting and nucleation (b) growth and consolidation, and (c) attrition and breakage (Thapa et al. 2019). Each stage is shown schematically in Figure 7. When the binder solution comes in contact with a dry powder mixture (wetting), the binder droplets penetrate the pores, forming nuclei (initial small particles). The wetting and nucleation stage is followed by collisions of granules, which results in granule compaction and growth. Finally, wet or dried granules break due to compact, shear, or compaction in the granulator, and attrition of granules leads to the formation of fine particles (Thapa et al. 2019, Verma et al. 2019).

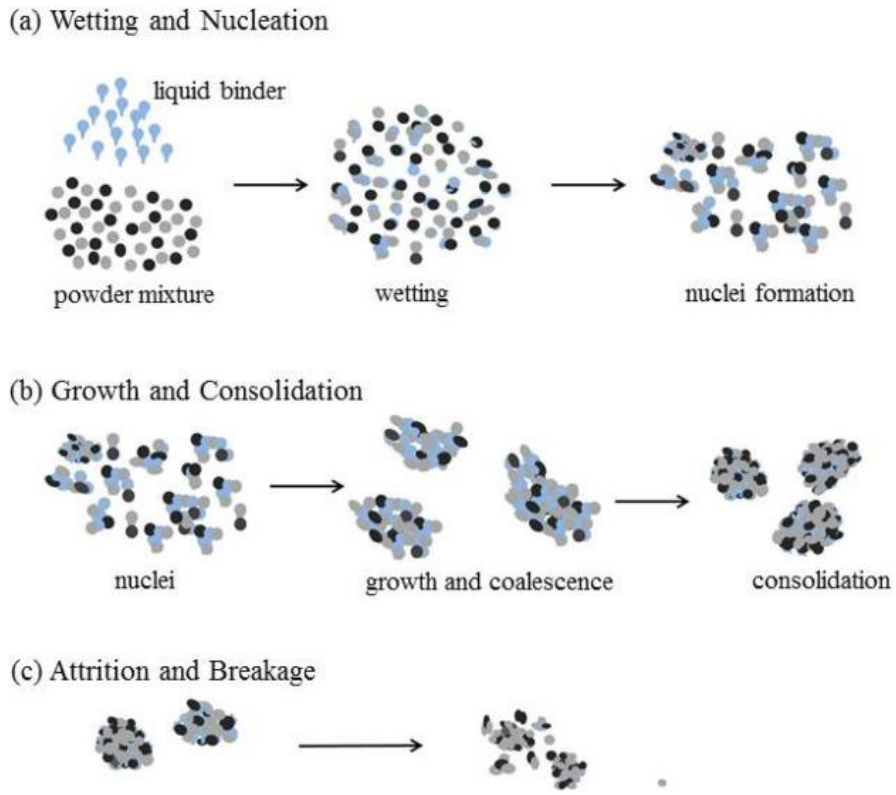


Figure 7. Schematic view of the granulation mechanism during wet granulation (Thapa et al. 2019).

Wet granulation can be conducted using a high-shear, low-shear or fluid-bed granulator (Badawy et al. 2019). High-shear wet granulation (HSWG) is one of the most popular wet granulation techniques. In comparison to other granulation methods, such as roller compaction or extrusion, HSWG method provides several advantages including shorter granulation time, greater densification of granules, less binding solution needed, narrow range of operating conditions, reduced process dust, and higher process reproducibility. Furthermore, HSWG is more feasible for highly cohesive, sticky materials containing hydrophilic compounds (Thapa et al. 2019). A high-shear wet granulation vessel consists of a granulating bowl, an impeller, a chopper, and a liquid binder addition (Thapa et al. 2019, Verma et al. 2019). In the HSWG process, a powder is dry mixed for a short period of time (5-15 min) at a low impeller speed to ensure that the mixture of APIs and excipients is homogenous. After the powder is well blended, a binder liquid is added by spraying or pouring on the powder mixture surface at a high impeller speed. Once the

binder has been added, impeller rotation is continued onto a step of kneading or wet massing. The wet granules are then sieved, dried, and milled for further processing.

The success of a wet granulation process, as well as the quality of final products, highly relies on the selection of suitable excipients and their composition. To design tablet formulations of new chemical entities or generics, it is necessary to thoroughly understand the properties of APIs and excipients, such as physicochemical properties of materials, deformation behaviour, morphology, particle size distribution, binder concentration, and binder solution surface tension (Hiremath et al. 2019, Thapa et al. 2019). The water-holding capacity of diluents, defined as the maximum amount of water used for wet granulation before paste formation, is also a critical attribute to consider when choosing excipients for HSWG. The following sections introduce the application of MCC as a pharmaceutical excipient in wet granulation.

2.6.2 MCC as a diluent/filler in wet granulation

MCC is one of the most widely used diluents in HSWG. It has water-insoluble yet hydrophilic properties with the ability to absorb different quantities of water at varying levels of humidity and excellent water imbibing or wicking action (Chaerunisaa et al. 2020, Dun et al. 2020, Saigal et al. 2009). Typically, MCC is used as a diluent and binder in dosage forms at a concentration ranging from 20% up to 90% by weight (Galichet 2006). High concentrations of MCC can enhance tablet hardness, affecting their disintegration and dissolution. When MCC is used as a diluent in wet granulation, the wicking action (water imbibition into the water compact) accelerates the wetting stage and makes the powder mix evenly wetted. Furthermore, the ability to retain water of MCC diminishes sensitivity to overwetting caused by excessive granulating liquid. The milling of the wet granulation will be easier because of fewer screen blockages, as well as the risks of case hardening, and uneven moisture distribution will be minimized. Case hardening is a phenomenon that occurs when the granules are dried at high speed under high temperature so that the granules seem dry from the outside, but the inside part remains wet. This phenomenon will lead to sticking and too soft tablets due to the water escaping the case-hardened granules when compressed (Chaerunisaa et al. 2020, Saigal et al. 2009).

MCC could be used alone as a filler in wet granulated tablet formulations. However, there are several concerns associated with using MCC as the only filler including deteriorated compactability upon wet granulation, lubricant sensitivity, speed sensitivity (compactability decreases at higher compression speeds and punch velocity), and loss of tablet tensile strength at higher humidity levels (hardness decay) (Badawy et al. 2006, Badawy et al. 2010, Shi et al. 2011b, Sun 2010, Thoorens et al. 2014). These problems could occur simultaneously when MCC is used as the sole filler in wet granulated formulations, affecting the overall compaction of formulations. Therefore, other fillers such as dicalcium phosphate dihydrate, lactose, and mannitol are often incorporated with MCC to make the formulation less susceptible to reduction in compactability. For example, in a study by Badawy et al. (2010) the combination of Avicel PH-102 and commercially available spray-dried mannitol 100SD at the ratio of 1:1 w/w was shown to reduce the susceptibility of the MCC formulation to compactability loss upon wet granulation. Additionally, the speed sensitivity index (SSI) was lower for the formulations with high levels of mannitol (SSI = 1.11. and 1.20) compared to those formulations without mannitol (SSI = 1.86 and 1.92). Hence, it can be concluded that the addition of mannitol would minimize the effect of compression speed on the compactability of an MCC formulation, providing a possibility to produce MCC-based tablets at higher compression speeds. The incorporation of mannitol with MCC was also found to reduce the sensitivity of tablets to loss of hardness upon storage at 25^{o}C/60% RH and facilitated particle size enlargement of the formulation during wet granulation (Badawy et al. 2010). This study recommends the inclusion of mannitol along with MCC instead of using MCC as the only filler to improve the tableting performance of the formulation in wet granulation.

2.6.3 MCC as a binder in wet granulation

MCC has exceptional binding properties thanks to its ability to deform plastically under pressure, relatively low bulk density, high surface area, and high hygroscopicity. When MCC is compressed, it undergoes plastic deformation, resulting in the maximization of the bonding area and the formation of numerous hydrogen bonds, which account for the cohesiveness and strength of compacts (Hiremath et al. 2019, Thoorens et al. 2014).

Moreover, the rapid wicking action of MCC is a huge advantage in high moisture granulations as it absorbs the excess water. According to Thoorens et al. (2014), potential critical material attributes, known as functionality-related characteristics, of MCC used as a binder include moisture content, particle size, size distribution, particle morphology, bulk density, specific surface area, DP, and crystallinity. Usually, MCC acts as a secondary binder in wet granulated formulations and can be used for granulating both soluble and insoluble powders (Saigal et al. 2009). When MCC is used as a binder at high concentrations, a disintegrant is recommended since the swelling of MCC in aqueous solutions will increase the viscous layer, which in turn affects the drug release (Hiremath et al. 2019).

2.6.4 MCC as a disintegrant

Disintegration is required in dosage forms to achieve intermediate drug release from oral tablets for absorption. Disintegrants act by five major mechanisms including swelling of disintegrants, porosity and capillary action (wicking), strain recovery, interruption of particle-particle bonds, and heat of interaction (Desai et al. 2016). Besides its functionalities as a filler and binder, MCC is also applied as a disintegrant in direct compressions and wet granulations. The mechanism for the disintegration action of MCC is suggested to be a combination of wicking and interruption of particle-particle bonds due to the presence of water. Swelling and recovery of elastic deformation are also proposed to contribute to the disintegration of MCC tablets. Regardless of these properties, the disintegration efficiency of MCC is relatively low and a high percentage of MCC up to 20% may be required to achieve adequate tablet disintegration (Desai et al. 2016, Moreton 2008). Recommended levels for MCC used as disintegrating agents in wet granulated formulations are around 5-20% (Chowhan 2020).

Avicel has a fast-wicking rate for water and small elastic deformation, thus it is often combined with superdisintegrants such as starch and croscarmellose sodium in order to achieve fast disintegration of orally disintegrating tablets. Combining Avicel with other disintegrants also helps in reducing loss in disintegration properties of wet granulated

Avicel during formulation (Chaerunisaa et al. 2020, Shihora and Panda 2011, Thoorens et al. 2014).

2.6.5 The change in the characteristics of MCC in wet granulation

Even though MCC has excellent compactability, it is known that the wet granulation process can cause a drastic reduction in MCC compactability (Badawy et al. 2006, Shi et al. 2011b, Wu et al. 2001b). The mechanism of MCC compactability loss when being subjected to wet granulation is not clearly defined. The compactability loss of MCC upon wet granulation is supposed to be related to the change in its characteristics. Different models have been presented to explain the behaviour of MCC during wet processing such as a crystallite-gel model (Kleinebudde 1997) or a sponge model (Ek and Newton 1998). Suzuki et al. (2001) studied the relationships between granulation, amounts of added water, and the mechanical strength of MCC granules produced by a high-shear mixer. In the study, the crystallite size of cellulose determined by a wide-angle X-ray diffraction method was found to decrease gradually with granulation time and increasing amounts of water added (Suzuki et al. 2001). Consequently, a change in crystallinity would influence the tabletability and compactability of MCC. Surface smoothing, densification, granule rounding, reduced surface area and reduced granule porosity during the HSWG process were also found to result in deterioration in tabletability and compactability of MCC. It has also been shown that lubrication with magnesium stearate may have a negative effect on compactability because magnesium stearate hinders bond formation during compression (Badawy et al. 2006, Osei-Yeboah et al. 2014, Shi et al. 2011b).

2.7 Aims of the study

The objective of this study was to investigate the properties and the feasibility of Aaltocell™ for tablet preparation. In this study, three grades of Aaltocell™ were evaluated and their properties were compared with a commercially available MCC, Vivapur 101. Vivapur 101 is a fine grade MCC, and it is commonly used as a pharmaceutical excipient in wet granulation, spheronization and capsule filling processes (Chaerunisaa et al. 2020, Galichet 2006). However, Vivapur 101 has poor flowability. In

the tablet formulation, paracetamol was used as an active pharmaceutical ingredient (API), and the amount of paracetamol in the formulation was 50%. Paracetamol is known for its poor compressibility, low flowability and it tends to cap during tablet compression (Martinello et al., 2006). Thus, it would be challenging to develop tablet formulations with a high amount of paracetamol for direct compression. To address this issue, the tablet formulations were high-shear wet granulated.

In the preliminary tests, two binders polyvinylpyroolidone (PVP) and hydroxypropylmethylcellulose (HPMC) were used at different concentrations in attempt to find the most suitable binder and its concentration for the tablet formulations. Corn starch was used as a disintegrant and silica as a glidant because they are the most common excipients for tablet preparation. After the wet granulation, Aaltocell^{TM} and Vivapur 101 formulations were investigated for particle size, morphology and flowability. Tablets were compressed using a rotary tablet press and then further characterized for physicochemical properties. In the quality tests, tablets were evaluated for friability, disintegration, uniformity of mass, uniformity of content and dissolution according to the requirements of European Pharmacopoeia.

3 MATERIALS AND METHODS

3.1 Preliminary experiment

Producing tablets with good qualities, such as disintegration, hardness, dissolution, and uniformity of mass, requires an ideal formulation, thus the concentration of excipients (filler, disintegrant, glidant, binder) are carefully selected based on the desired properties of the final product. The purposes of the preliminary tests were to first design a formulation that would produce granules with good tabletability and paracetamol tablets with rapid disintegration and adequate hardness to pass the friability test set by European Pharmacopoeia. In the preliminary test, a total of eight different formulations were made using two binders, PVP K300 and HPMC, to discover which binder would provide optimal manufacturability of tablets at a certain concentration. 50% (w/w) of paracetamol was used as an active substance and Vivapur 101 was used alone as a reference filler in

all eight formulations. During the test, the percentage of the disintegrant, corn starch, was increased from 5.1% to 7% to achieve faster tablet disintegration (Tables 3 and 4).

The final tablet formulation was selected based on the results of flowability of granules, uniformity of mass, friability and disintegration tests. This formulation was then chosen for producing paracetamol tablets by replacing Vivapur 101 with three different Aaltocell^{TM} grades to compare the influence of Aaltocell^{TM} with Vivapur 101 on tablet properties after high-shear granulation.

Table 3. Formulations containing PVP used in pre-tests.

	Material	**Grade / manufacturer**	**Role**	**Amount (%)**			
PVP used as the binder	Paracetamol	USP, Hawkins inc., USA	API	50	50	50	50
	Microcrystalline cellulose	Vivapur 101 (JRS Pharma, Germany)	Filler	40.4	39.4	38.4	36,6
	PVP	K30 (BASF, Germany)	Binder	4	5.9	6,9	5,9
	Corn starch	Starch 1500 (National Chemical, USA)	Disintegrant	5,1	5,1	5,1	7
	Silica	Aerosil 200 (Evonik Degussa Corp., Parsippany, USA)	Glidant	0,5	0,5	0,5	0,5

Table 4. Formulations containing HPMC used in the pre-test

	Material	Grade / manufacturer	Role	Amount (%)			
HPMC used as the binder	Paracetamol	USP, Hawkins inc., USA	API	50	50	50	50
	Microcrystalline cellulose	Vivapur 101 (JRS Pharma, Germany)	Filler	40.4	38.4	37.4	35.5
	HPMC	K100M (Dow Chemical Company, USA)	Binder	4	6	7	7
	Corn starch	Starch 1500 (National Chemical, USA)	Disintegrant	5,1	5,1	5,1	7
	Silica	Aerosil 200 (Evonik Degussa Corp., Parsippany, USA)	Glidant	0.5	0.5	0.5	0.5

The granules produced with these formulations were measured for bulk- and tapped density according to European Pharmacopoeia and Carr's index was calculated to classify their flowability (Table 5). The measurement of bulk and tapped density would be described in detail in section 3.4.2 Bulk-, tapped and true density.

Table 5. Bulk- and tapped density of PVP and HPMC formulations and their flowability according to Carr's index.

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Flowability
PVP 5.9% & starch 7%	0.468 ± 0.005	0.527 ± 0.007	13.1	Good
PVP 6.9% & starch 5.1%	0.433 ± 0,011	0.505 ± 0.011	14.3	Good
PVP 5.9% & starch 5.1%	0.426 ± 0,006	0.507 ± 0.011	15.9	Good
PVP 4% & starch 5,1%	0.399 ± 0.004	0.479 ± 0.008	16.8	Fair
HPMC 7% & starch 7%	0.455 ± 0.007	0.570 ± 0.006	20.3	Fair
HPMC 7% & starch 5.1%	0.443 ± 0.007	0.598 ± 0.008	25.8	Passable
HPMC 6% & starch 5.1%	0.430 ± 0.005	0.593 ± 0.003	27.4	Poor
HPMC 4% & starch 5.1%	0.423 ± 0.002	0.584 ± 0.011	27.5	Poor

Two formulations containing each PVP and HPMC as binders with the best flowability properties were chosen for further testing purposes, i.e.:

1. PVP with 5.9% & starch with 5.1%,
2. PVP with 5.9% & starch with 7%,
3. HPMC with 7% & starch with 7%, and
4. HPMC with 6% & starch with 5.1%.

From the four formulations mentioned above, tablets were compressed to a target weight of 220 – 230 mg. The high-shear wet granulation and tableting process that was conducted in the preliminary test will be described in detail in sections 3.2. High-shear wet granulation and 3.3. Tablet compression. In the pre-test, the tablet press was run for 20 rounds, and approximately 5 tablets were discarded before collecting tablets to ensure the uniformity of tablets. Because of the complexity of the European Pharmacopoeia tests,

three preliminary tests, including uniformity of mass of single-dose preparations, disintegration and friability, were conducted to evaluate the tablet properties. The results of these pre-tests are presented in Table 6.

Table 6. Property and test results of the tablet formulations in the preliminary test

Property/test	**PVP 6,9 % & starch 5,1%**	**PVP 5,9% & starch 7%**	**HPMC 6% & starch 5,1%**	**HPMC 7% & starch 7%**
Weight (mg) n = 20	210.8 ± 3.9	221.7 ± 1.3	212.1 ± 2.2	226.4 ± 3.5
Crushing strength (N) n = 10	1021 ± 11.7	89.8 ± 5.2	88.7 ± 4.9	96.2 ± 4.4
Uniformity of mass of single dose	Pass The maximum individual weight deviation 3.3%	Pass The maximum individual weight deviation is 0.95%	Pass The maximum individual weight deviation: 2,2%	Pass The maximum deviation from the average mass is 3,2%
Disintegration n = 6	Pass Disintegration time: 6 minutes	Pass The tablets disintegrated rapidly within 1 minute	Pass Disintegration time: 5 minutes	Fail The tablets disintegrated more slowly compared to other formulations. Disintegration time 25 minutes
Friability	Pass Weight loss: 0.30%	Pass Weight loss: 0.31%	Pass Weight loss: 0.30%	Pass Weight loss: 0.30%

The paracetamol tablets made with the formulation containing 5.9% of PVP and 7% of starch disintegrated rapidly within a minute, and the weight loss after the friability test was only 0,3%. Moreover, these tablets had the lowest individual weight variation, 0.95%. Thus, this formulation was selected for producing paracetamol tablets with AaltoCell^{TM}. This study examined three types of AaltoCell^{TM} (Aalto University, Espoo, Finland) and Vivapur 101 was used as a reference MCC. Components of the final formulations containing AaltoCell^{TM} MCCs are shown in the Table 7 below. Distilled water obtained from an in-house Milli-Q-Millipore system (Merck KGaA, Darmstadt, Germany) was used as a granulation liquid throughout the whole study.

Table 7. Components of the formulations investigated in the present study

Sample	Formulation components
V1	Paracetamol 50%, PVP 5.9%, starch 7%, silica 0.5 %, Vivapur 101 36.6%
A1	Paracetamol 50%, PVP 5.9%, starch 7%, silica 0.5, AaltoCell^{TM} A 36.6%
B1	Paracetamol 50%, PVP 59%, starch 7%, silica 0.5, AaltoCell^{TM} B 36.6%
C1	Paracetamol 50%, PVP 5.9%, starch 7%, silica 0.5, AaltoCell^{TM} C 36.6%

3.2 High-shear wet granulation

750 g of high-shear wet granulation formulation was transferred into a 4L metallic bowl of a high-shear wet granulator (Figures 8 and 9) and then pre-mixed for 1 minute at a chopper speed of 1500 rpm and impeller speed of 1000 rpm. After the pre-mixing, 150 mL distilled water was added to the mixture through the spray nozzle located on the top of the granulator cover using three 60 mL syringes. The speed of the chopper and impeller was kept constant during the water addition to the mixture. The granulation was continued until a rapid increase in torque was observed.

Figure 8. High-shear wet granulator used in this study (Diosna P 1-6, Dierks & Söhne Gmbh, Osnabrück, Germany).

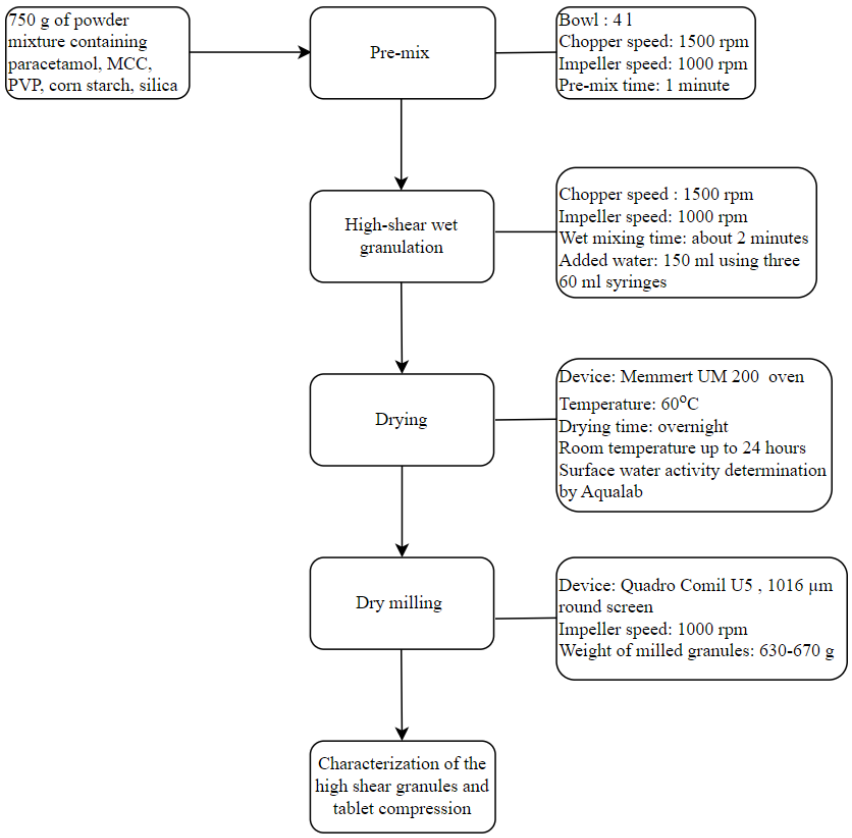


Figure 9. A schematic representation of high-shear wet granulation and the parameters used in this study.

After the granulation, the granules were tray dried in Memmert UM 200 (Memmert GmbH, Schwabach, Germany) oven at the temperature of 60ºC overnight. When the granules were dry, they were left on trays at room temperature for about 24 hours. The water activity of the granules was measured using an AquaLab device (Decagon Devices Inc., Washington, USA) to ensure that the granules were well dried before storing them in plastic bags. The target surface activity for dry granules was 0,005 A_w.

Then the dried granules were milled using a Quadro Comil U5 conical screen mill equipped with a 1016 µm-grater hole screen (Figure 10). The speed of the impeller was set to 1000 rpm. All high-shear granules were milled with only one size of the screen. The weight of the milled granules was in the range of 630 – 670 g.

Figure 10. The Quadro Comil U5 mill used for dry milling in this study.

3.3 Tablet compression

The powder blends were spread on trays and stored in a tableting room with the relative humidity of 40-51% before tablet compression. The tableting of all formulations was conducted in the same premises and conditions to minimize the effect of environmental variables on the characteristics of tablets. The relative humidity during the tableting was 50.6% and the temperature was 21.5ºC. The powders were compressed into tablets using

a Ronchi AM 13/8 -rotary tablet press (Officine Meccaniche F.lli Ronchi, Milano, Italy). Three out of eight stations in the tablet were equipped with single punches of 9.0 mm diameter. The powders were loaded into the machine via a gravity feeder. The target tablet weight was set to 230 mg and the target crushing strength of the tablets was 110 N. Initially, a few tablets were collected to weigh and measure the crushing strength to adjust the die filling and the compression force. In addition, the tablets were put into a glass of water to observe their disintegration. When suitable process parameters for tableting were identified, the rotary tablet press was run for 60 rounds to compress tablets. The compression speed was kept constant at around 16.5-16-6 rpm for all formulations. There was no pre-compression force used and the lower as well as the upper punch force were recorded during the compression. The tablet samples were collected at the beginning (round 1-20), the middle (round 21-40) and the end (round 41-60) of the tableting, and then evaluated for their physicochemical properties. During tableting, approximately 5 tablets were discarded in the beginning to obtain uniform tablets with the target weight and the crushing strength.

3.4 Characterization of high-shear granules

The test methods used in the characterization of granules are summarized in Table 8.

Table 8. Methods chosen for the characterization of the high-shear granules.

	Property	**Test method**
High-shear granules	Particle size distribution	Parsum Inline Particle Probe Serie IPP 70
	Bulk- and tapped density	European Pharmacopoeia 2.9.34
	True density	Helium pycnometer
	Flowability	European Pharmacopoeia 2.9.36 (angle of repose, Carr's index and Hausner ratio) Image-based analysis
	Morphology	Polarized light microscopy

3.4.1 Particle size distribution

The particle size distribution analysis was carried out using Parsum Inline Particle Sizing Probe IPP 70 (Parsum GmbH, Chemnitz, Germany). Each formulation was analysed three times. The D_{10}, D_{50} and D_{90}-values obtained from the three measurements were averaged and the width of distribution (span-value) was calculated using the following equation:

$$span = \frac{(D_{90} - D_{10})}{D_{50}}$$

3.4.2 Bulk-, tapped and true density

All powder blends were stored in the test room with a relative humidity of 23 - 25% and temperature of 22°C for several days before the measurement of density and angle of repose. The bulk and tapped density were measured according to the European Pharmacopoeia 11.0 (2.9.34. Bulk and tapped density of powder) method. A 100 g sample of the test powder was gently introduced through a funnel into a dry, graduated 250 ml cylinder, and the powder was necessarily levelled without compacting. The untapped apparent volume (V_0) was read to the closest graduated unit. After measuring V_0, the same cylinder with the sample was placed on the Erweka SVM tapped density tester (Erweka Gmbh, Germany) and tapped for 10, 490 and then 750 times. The corresponding volumes of 10 (V_{10}), 500 (V_{500}) and 1250 (V_{1250}) taps were recorded. Whether the difference between V_{500} and V_{1250} was more than 2 mL, the procedure was continued for another 1250 taps or until the difference between subsequent measurements was less than or equal to 2 ml. Finally, the bulk and tapped densities were calculated by dividing the mass of the sample with the untapped volume (V_0) or tapped volume (V_f). Each formulation was measured in triplicate and the average value of three measurements was calculated. The compressibility index (Carr's index) and Hausner ratio were determined by using the apparent and tapped volumes to classify the flowability of the powders:

$$Hausner\ ratio = \frac{V_0}{V_f}$$

$$Carr's\ index = 100x\frac{V_0 - V_f}{V_0}$$

where V_0 is the untapped apparent volume and V_f is the final tapped volume

The true density of the materials was determined using a Micromeritics 1305 helium pycnometer (Multivolume pycnometer 1305, One Micromeretics, USA). The sample cup was filled with ½ of the powder blend and was accurately weighed before and after the measurement. Before measuring the true density, helium was allowed to flow through each sample by increasing and decreasing the flow pressure 8-10 times to remove possible moisture from the samples. Pressure values were allowed to stabilize before recording and used to calculate the true volume of the samples. Three measurements of each formulation were performed, and the average true density was defined by dividing the mass of the sample by its true volume.

3.4.3 Angle of repose

In this study, the determination of the angle of repose (AoR) was used to evaluate the flow properties of the powders. The procedure was performed according to the European Pharmacopoeia 11.0 (2.9.36 Powder flow). The powder was allowed to fall through a plastic funnel on a flat plastic disc with a fixed diameter of 3.7 cm and a protruding outer lip to retain a base of powder. The funnel was kept at approximately 2-4 cm above the top of the powder pile while being formed to minimize the impact of falling powder on the peak of the powder cone. Once the powder formed a symmetrical cone and started to flow over the base, the height of the cone was measured with a ruler. The measurement was done in triplicate. The AoR (θ) was calculated using the following equation:

$$tan(\theta) = \frac{height}{0.5\ x\ base}$$

Based on the obtained values of AoR, the flowability of the powders was classified: the flow is considered to be excellent if the AoR is less than 30 degrees, and poor when the AoR is above 45 degrees

3.4.5 Image-based characterization of powder flow

Besides the compressibility index, Hausner ratio and AoR, the powder flow was determined by image-based analysis using a novel small-scale measuring device developed by Blanco et al. (2020). The testing device set-up and diagram of the measurement cuvette are shown in detail in Figure 11.

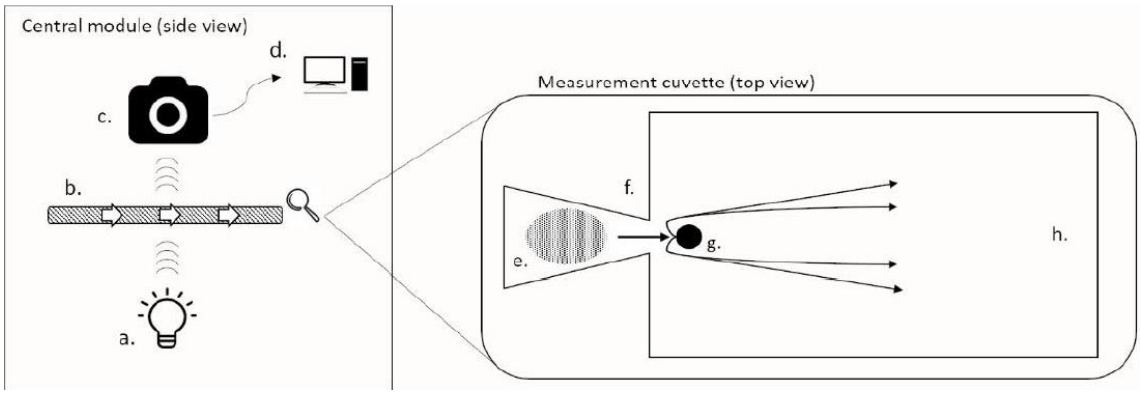


Figure 11. Scheme of the side view of the image-based powder flow measuring device (left image) and the top view of the measurement cuvette (right image). **a**. Light source **b**. Sample cuvette **c**. Camera module **d**. Computer, data acquisition **e**. Loading chamber **f**. Orifice g. Disturbance pivot, and **h**. Analytical chamber. White arrows show the direction of movement of the device and black arrows show the powder flow inside the cuvette (Blanco et al., 2020).

A small amount of the powder (in milligrams) was placed in the loading chamber. Then, the powder sample was first subjected to a positive acceleration (slow acceleration) and subsequently, a higher negative acceleration which triggered the movement of the powder from the loading chamber to the analytical chamber via the orifice (fast deceleration phase), creating unique flow patterns for each powder sample (Blanco et al., 2020). The motion profile is depicted in Figure 12. Images of these flow patterns were captured and the flowability index (FI%) was recorded and compared with the Carr's index. The measurements were performed in a RH of 40.7 – 43.2% and temperature of 22.4 – 23.5ºC. Also, raw materials, including paracetamol and ungranulated MCCs were determined for FI% to examine the impact of granulation on powder flow.

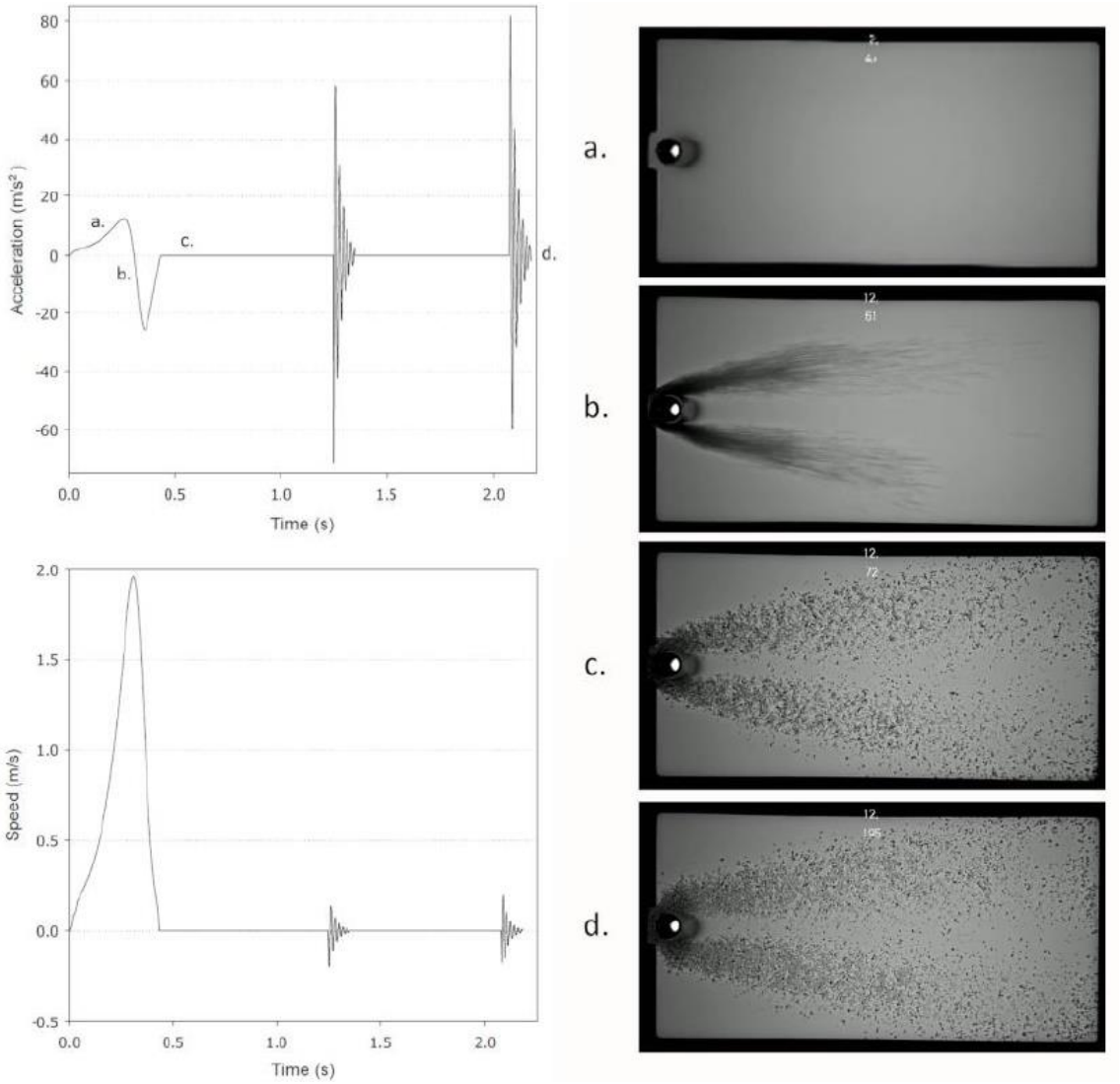


Figure 12. Different phases of the motion profile inside the measurement cuvette. **a**. resting state/zero speed – Low acceleration **b**. Fast deceleration **c**. First static state, and **d**. Second static state – Image capturing (Blanco et al., 2020)

3.4.6 Morphology

Particle shape and morphology were visualized by polarized light microscopy (PLM). Before the analysis, the glass slides were carefully rinsed with distilled water followed by ethanol and dried with lens cleaning tissue. A small amount of the granule or raw material was spread into a thin layer on a glass slide and then analysed at 10x, 20x and 50 magnifications. Images of particle shape were captured for further analysis.

3.5 Characterization of tablets

Before further characterization of tablet properties, the tablets were allowed to rest overnight to undergo full viscoelastic recovery. Dimensions and breaking force of the tablets were measured to calculate tablet tensile strength. European Pharmacopeia tests were carried out to evaluate the quality of the final products prepared from different MCCs (Table 9).

Table 9. Methods chose for the tablet characterization in this study.

	Property	**Test method**
Tablets	Uniformity of mass of single-dose preparations	European Pharmacopoeia 2.9.5
	Dimensions	Diameter and height measurement
	Breaking force → tensile strength	Tablet hardness tester
	Friability	European Pharmacopoeia 2.9.7
	Disintegration	European Pharmacopoeia 2.9.1
	Uniformity of content of single-dose preparations	European Pharmacopoeia 2.9.6
	Uniformity of dosage units	European Pharmacopoeia 2.9.40
	Dissolution	European Pharmacopoeia 2.9.3, paddle method

3.5.1 Tablet dimensions, breaking force and tensile strength

Ten tablets of each formulation from the first and final stages of the tableting process were randomly selected to measure tablet thickness and diameter using a digital indicator (Sony U-30F digital indicator, Sony Megascale, Japan). Subsequently, the breaking force of the tablets was determined by a tablet hardness tester (Erweka TBH 125, Erweka GmbH, Germany). When measuring the breaking force, the tablets were oriented with their scores parallel with the direction of movement. From the tablet thickness, diameter and breaking force, the tensile strength was calculated using the following equation:

$$\sigma = \frac{2F}{\pi DH}$$

where F is the breaking force, D is the tablet diameter and H is the tablet thickness (Newton and Fell 1970).

3.5.2 Friability

The friability test was performed according to the European Pharmacopeia 11.0 test 2.9.7 Friability of uncoated tablets by a friability tester (PharmaTest PTF R, Pharma Test Apperatebau AG, Germany). As near as possible 6.5 g of tablets, which corresponded to 27-29 whole tablets, was taken randomly for each formulation from the initial, middle and final stages of the tableting process. Each sample tablet was cautiously dedusted and weighed before testing. The tablets were put in the tester and rotated for 100 rounds at a rotation speed of 25 rpm. Subsequently, the tablets were removed from the tester, dedusted and weighed again. The friability percentage was calculated by applying the following formula:

$$Friability\ (\%) = \frac{initial\ weight - final\ weight}{initial\ weight} \times 100$$

The test was run only once for all formulations. Tablets are considered to have acceptable durability if a maximum weight loss (friability percentage) is not greater than 1.0%.

3.5.3 Uniformity of mass

In the test for uniformity of mass, 20 tablets selected randomly from the initial, middle and final stages of the tableting process were weighed individually as per the European Pharmacopoeia 11.0 test 2.9.5 Uniformity of mass of single-dose preparations. The average mass of the tables was determined and individual mass deviation from the average value was calculated in percentage.

3.5.4 Uniformity of content

To determine the paracetamol content in the compressed tablets, phosphate buffer pH 7.2 was prepared according to European Pharmacopoeia 11.0 5.17.1. Recommendations on dissolution testing, and used as dissolution media for content uniformity analysis and dissolution test. Ultraviolet (UV) spectrophotometry was selected as an appropriate analytical method to determine the individual contents of paracetamol. To prepare the standard solutions of paracetamol, 110 mg paracetamol was dissolved in 1000 ml of phosphate buffer pH 7.2. A series of 12 dilutions were made from this stoc solution. The dilutions were filtered through a 0.2 µm cellulose acetate membrane filter (VWR International bvba, Belgium) and absorbance of the solutions was determined by UV-Vis spectrophotometry at a wavelength of 243 nm (UV-1600PC, VWR International bvba, China). The filter was moistened with phosphate buffer before filtering each solution and changed between every dilution. The absorbance of each sample was plotted as a function of concentration to generate a standard curve (APPENDIX 1), which was also used to determine the concentrations of samples in the dissolution tests.

The uniformity of content test was carried out for 10 tablets as per the European Pharmacopoeia 11.0: 2.9.6. Uniformity of content of single-dose preparation. For all four formulations, three tablets from the initial, three tablets from the middle and four tablets from the final stage of the tableting were randomly taken and weighed individually. Each tablet was crushed, dissolved and mixed to 250 ml of phosphate buffer pH 7.2 using a magnetic stirrer and left to stand overnight. Subsequently, 5 ml of this stock solution was diluted to 250 ml with phosphate buffer pH 7.2 and then analysed for the absorbance at a wavelength of 243 nm by a UV spectrophotometer. The samples were filtered through a 0.2 µm cellulose acetate membrane filter (VWR International bvba, Belgium), which was changed after each sample. Based on the measured absorbances, the paracetamol content of each tablet was determined whether it was within the limits of 85 – 115% of the average content (European Pharmacopoeia 11.0: 2.9.6. Uniformity of content of single-dose preparations). Additionally, the acceptance value was calculated referring to the European Pharmacopoeia 11.0: 2.9.40: Uniformity of dosage units.

3.5.5 Dissolution tests

Dissolution tests for all four formulations were conducted as per the European Pharmacopoeia 11.0: 2.9.3. Dissolution test for solid dosage forms using the paddle apparatus. Two tablets were taken at random from each stage of the tableting process and accurately weighed. 900 ml of phosphate buffer pH 7.2 was poured into the glass vessel and equilibrated in the water bath to 37±0.5^{o}C. Paddles were attached to the dissolution testing equipment (Distek Dissolution System 2100C, Distek Inc., North Brunswick, USA) and the paddle rotation was set to 75 rpm. 5 ml of sample was withdrawn at 1, 3, 5, 10, 20, 30, 45 and 60 min and each aliquot withdrawn was replaced with an equal amount of fresh dissolution medium at 37±0.5^{o}C. The samples were diluted to 50 ml with phosphate buffer pH 7.2 and the paracetamol concentrations were determined by measuring the absorbance at a wavelength of 243 nm using a UV-Vis spectrophotometer (UV-1600PC, VWR International bvba, China). Before the analysis, each sample was filtered through a 0.2 µm cellulose acetate membrane filter (VWR International bvba, Belgium) to remove undissolved particles.

3.5.6 Disintegration

Disintegration test was implemented as per the European Pharmacopoeia 11.0: 2.9.1. Disintegration of tablets and capsules using a basket-rack assembly attached to a Sotax DT3 disintegration tester (Sotax AG, Allschwill, Switzerland). Six tablets for each formulation were randomly selected from the initial, middle and final stages of the tableting process. Each tablet was placed in the open-ended tube of the basket and covered by a perforated plastic disk. Purified water was used as the immersion fluid and the temperature was maintained at 37±0.5^{o}C. During the procedure, the basket was automatically raised and lowered in the immersion fluid at a rate of 30 cycles per minute. The tablets were visually observed until they were completely disintegrated, and the disintegration time of each tablet was recorded using a separate timer. A tablet was regarded to be completely disintegrated when there was no longer a firm core existed.

4 RESULTS AND DISCUSSION

4.1 Particle size and morphology

The appearance of all four high-shear wet granulated formulations after dry milling is shown in Figure 13.

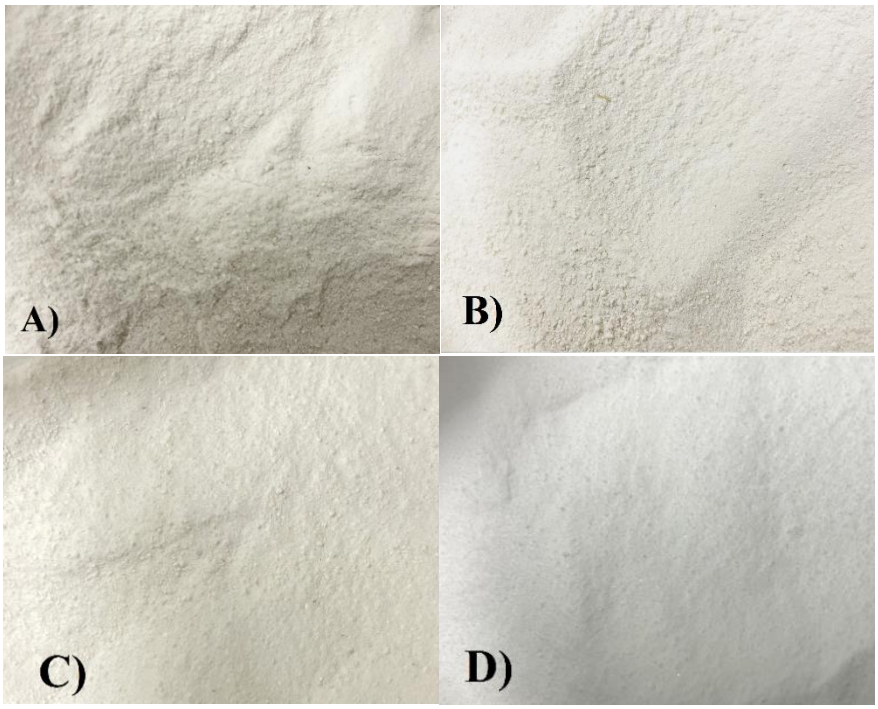


Figure 13. High-shear granules after dry milling by Quadro Comil 1.0 mm round-holed grater screen. **A)** A1, **B)** B1, **C)** C1 and **D)** V1 granules.

The D_{50} particle size of the granules was in a range of 85 to 318 µm (Table 10). After the high-shear wet granulation process, the B1 formulation formed larger granules and its granule size was less uniform compared to the other formulations (Figure 14). Therefore, it is not surprising that B1 granules are the coarsest among all formulations with a D_{50} particle size of 318 µm and is classified as moderately fine according to European Pharmacopoeia (2.9.35. Powder fineness). B1 was also the only formulation that had oversized granules (above 1.0 mm) (Table 10, Figure 15). However, the amount of large granules in B1 was very small (< 1%) and the amount of fine particles (under 0.45 mm) was insignificant. The difference in particle size between the formulations might be caused by the subjectivity and inaccuracy involved in identifying the endpoint during

high-shear wet granulation. In this study, the endpoints were determined only by observing changes in the power consumption of the mixer, which could lead to different wet massing times between the formulations. One of the reasons why B1 generated larger granules could be its longer wet massing time, which was 130s, compared to other formulations (110 – 120 s). Wet massing time has been found to have a strong correlation with the granule properties in previous studies. Longer massing time usually generates granules with larger particle diameters (Hegedũs and Pintye-Hódi 2007, Ohno et al. 2007, Thapa et al. 2019).

Table 10. Particle size distribution and their fineness of the four MCC formulations in this study.

Formulation	**D10 (µm)**	**D50 (µm)**	**D90 (µm)**	**Span**	**Fineness**	**Particles above 1.0 mm (%)**	**Particles under 0.45 mm (%)**
A1	62±0.4	85±6.8	261±24	2.35	Very fine	0	0.53
B1	77±0.8	318±35	740±97	2.09	Moderately fine	0.97	0.27
C1	67±0.3	161±3.9	644±25	3.58	Fine	0	0.6
V1	60±0.5	90±3.8	292±14	2.58	Very fine	0	0.8

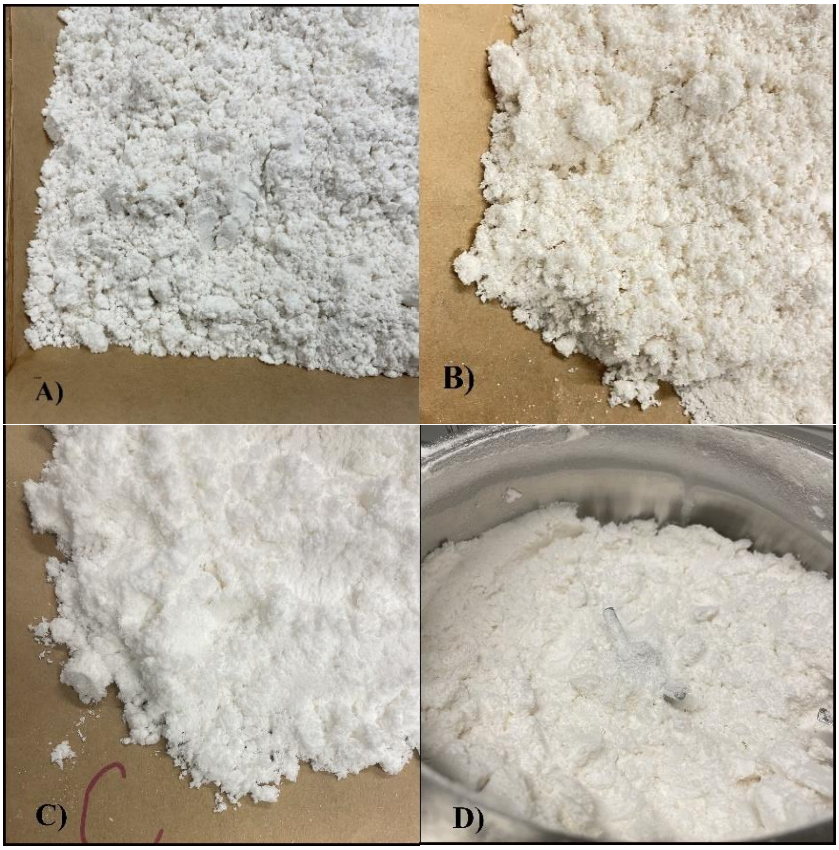


Figure 14. Granules shortly after the high-shear wet granulation before tray drying in an oven. A) A1, B) B1, C) C1 and D) V1 granules. When examining these granules visually and by hand, the B1 formulation showed to form larger and harder granules.

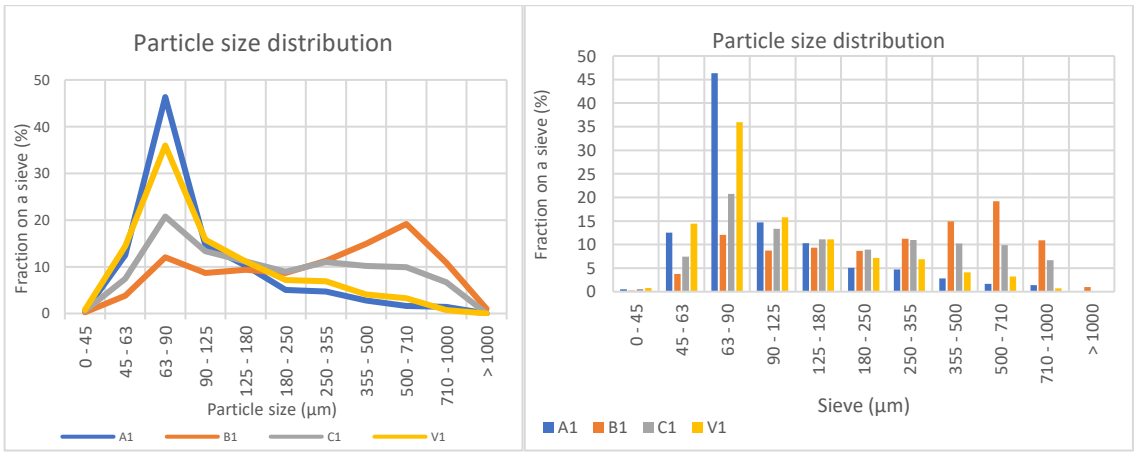


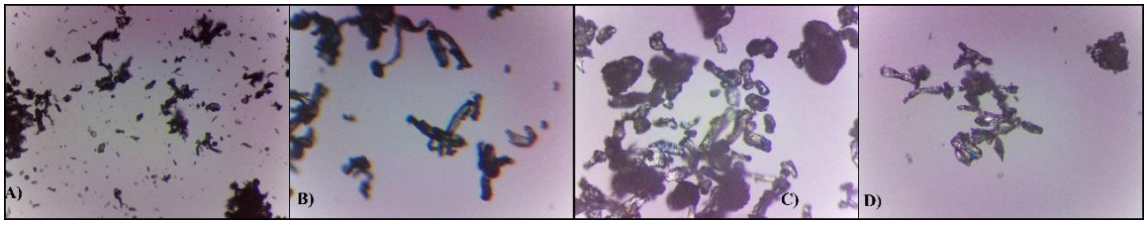
Figure 15. a) Particle size distribution of the formulations (n=3) and b) histogram of the particle size distribution (n=3).

Three out of four formulations including A1, B1 and V1 had quite similar particle size distribution with the span values varying from 2.09 to 2.58 (Table 10). Meanwhile, the C1 formulation possessed a wide particle size distribution (span value 3.58). The broad particle size distribution of the C1 formulation might result from the batch loading of the mill, which is also regarded as fill level. The high fill level of the mill could prolong the residence time of granules and thereby resulting in an increased amount of smaller particles (Kotamarthy et al, 2020).

Among the four formulations, A1 and V1 had the highest fraction in the sieve size of 63 – 90 µm. It was surprising that A1 and V1 were very fine formulations with D50 particle size of 85 µm and 90 µm, respectively, even though the high-shear wet granulation of these formulations was performed using the same amount of water as granulation liquid and the duration of wet massing was 118-120 s compared to 115 s for C1. This shows that the wet granulation of A1 and V1 might require longer granulating time to generate granules with a larger particle size. Moreover, different grades of MCC have different water uptake capacities and thus, A1 and V1 formulations could in the future be further studied to optimize the L/S ratio (liquid-solid ratio) to obtain larger final granules. Higher amount of granulation liquid results in increased agglomeration as there is more liquid available to promote nucleation of fine powders, and an inadequate amount of granulation liquid leads to drop coalescence and a high percentage of ungranulated powder (Badawy et al, 2000; Chitu et al, 2011, Parikh 2009, Thapa et al, 2019).

PLM analysis was carried out to study the morphology of the MCCs used in this study and the granules after milling. PLM pictures showed clearly the differences in size between the MCCs (Figure 16). Based on the analysis, the MCC particles were non-homogeneous and exhibited an elongated fibrous shape. AaltoCell^{TM} A powder consisted of more fines and short rod-shaped particles. After the granulation, the particles were still mostly elongated, but they were more uniform in size and shape (Figure 17). There was a fraction of fine particles detected in sample A1, which might be ungranulated material. This could explain why the A1 formulation had the smallest particle size among these four formulations.

a)



b)

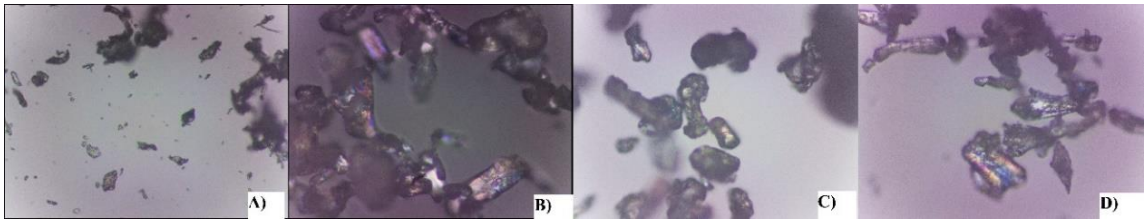


Figure 16. PLM pictures of MCC powders at a) 10x magnification and b) 20x magnification. **A)** AaltoCell^{TM} A **B)** AaltoCell^{TM} B **C)** AaltoCell^{TM} C and **D)** Vivapur 101 powder.

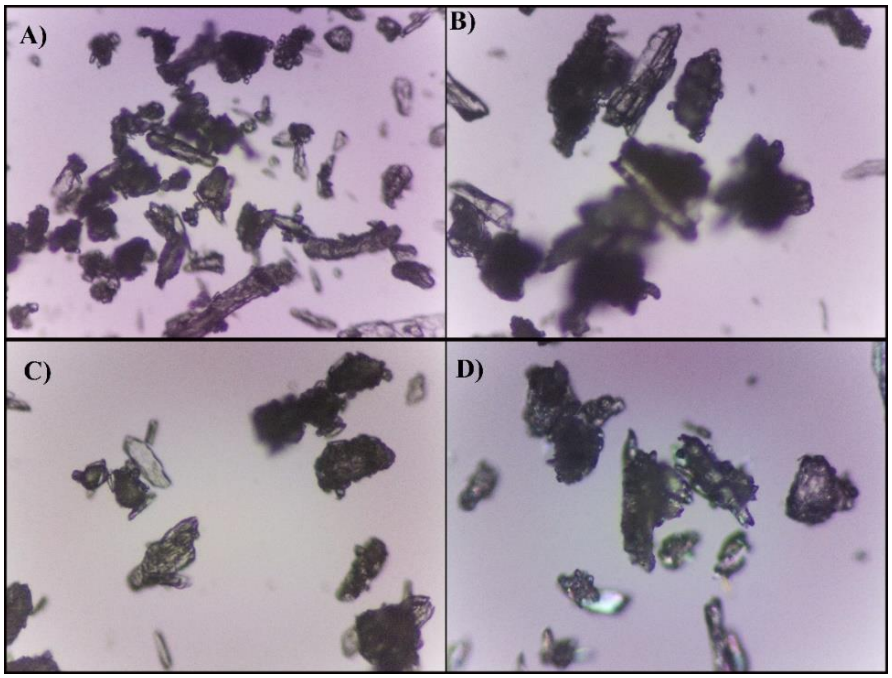


Figure 17. PLM pictures of the granules after dry milling through a 1016 µm round-holed grater screen. **A)** A1, **B)** B1, **C)** C1 and **D)** V1 granules. Pictures were taken at 10x magnification.

Particle size and shape have significant impacts on powder flow. In general, particles with larger particle size and spherical shape appear to have greater powder flowability than small and irregular ones (Goh et al. 2018; Horio et al, 2014; Xiu et al, 2020). Small particle size is expected to flow poorly, having high angle of repose, long avalanching time and increased cohesion (Goh et al, 2018; Krantz et al, 2009; Thalberg et al, 2004). Usually, particles larger than 250 µm are considered to be free-flowing, while particles smaller than 10 µm are very cohesive (Goh et al, 2018; Staniforth 2002). When the particle size is decreased, the specific surface area to volume ratio is higher, causing the interparticulate cohesion to dominate the bulk flow and thus enhancing the shear resistance (Shi et al, 2017). Besides particle size, particle shape is also an essential determinant of powder flowability. Powders with similar particle sizes but different particle shapes can exhibit different flow behaviour due to variations in interparticle contact areas. Sphericity and smooth surface of particles minimize contact areas between particles, resulting in greater powder flowability, while irregular particles have a relatively high surface-to-volume ratio and therefore poor powder flow (Standiforth 2002). Horio et al. (2014) also observed that higher sphericity of particles resulted in larger angle of repose for MCC. Thus, the A1 formulation was expected to have the poorest flowability among the four formulations in this study due to its small granule size, excess fine particles and irregular shape.

4.2 Densities and flow properties

Bulk density is the ratio of the mass of an uncompacted powder to its volume which includes the interparticulate voids as well as the envelope volumes of the particles (Amidon et al, 2009). The bulk density of a powder is always smaller than its true density and the bulk density of a material can vary depending on its porosity and particle packing (Staniforth 2002).

In contrast to the bulk density, the true density of a powder is the ratio of the mass of the powder divided by its volume, excluding all pores, and internal and external voids (Amidon et al. 2009). In theory, a material can only have a single true density value regardless of what method is applied to measure its true density. The true density can be

determined using three methods including gas pycnometry, liquid displacement and flotation.

Tapped density is defined as the ratio of mass and tapped volume, which is achieved after tapping the powder for a certain time (Amidon et al. 2009). The tapped density of a material reveals its maximum packing density obtained under the influence of tapping. As tapped density is dependent on several factors including particle size distribution, particle shape and surface roughness, it is often linked to the flow properties and compressibility. In general, a powder with more regularly shaped particles (i.e., rounded or spherical particles) possesses higher tapped density than particles with irregular shape, such as flaky, needle-like or rod-like particles.

Powder flowability is an essential parameter in the formulation design and development of oral solid dosage forms. Powder flow behaviour during tablet manufacturing has a significant impact on die filling, which then affects aspects of tablet quality such as weight variation, content uniformity, breaking strength and disintegration (Goh et al, 2018; Sun 2010). Adequate powder flow contributes to rapid and homogeneous die filling, ensuring uniformity of content and consistency in tablet properties. Thus, gaining insights into the flowability of tablet formulations is critical to avoid possible hurdles related to powder flow.

In this study, the MCC powders as well as the high-shear wet granulated formulations were measured for bulk, tapped, and true density. Moreover, their flow properties were assessed by Carr's index, Hausner ratio, angle of repose, and image-based analysis. The results obtained are summarized in Tables 11 and 12.

Table 11. Flow properties of the MCC powders and high-shear wet granulated formulations used in this study. The bulk and tapped densities were measured in triplicate (n=3) and the flowability index once (n=1).

Sample	Bulk density (g/ml)	Tapped density (g/ml)	Hausner ratio	Carr's index	Flowability (HR and CI)	AoR (°)	Flowability (AoR)	FI%
AaltoCell™ A	0.28	0.46	1.64	39.3	Very, very poor	No flow	-	3.02
AaltoCell™ B	0.31	0.44	1.42	29.7	Poor	No flow	-	1.18
AaltoCell™ C	0.47	0.65	1.38	27.7	Poor	No flow	-	5.62
Vivapur 101	0.30	0.42	1.39	28.3	Poor	No flow	-	3.09
A1	0.42	0.52	1.21	17.8	Fair	38.0	Fair (aid not needed)	11.5
B1	0.48	0.56	1.14	12.6	Good	33.0	Good	4.74
C1	0.49	0.57	1.17	14.4	Good	33.9	Good	8.27
V1	0.45	0.56	1.22	18.1	Fair	37.5	Fair (aid not needed)	7.87

Table 12. True densities of the MCC powders and high-shear wet granulated formulations used in this study (n=3).

Sample	True density (g/ml)
AaltoCell™ A	1.58 ± 0.014
AaltoCell™ B	1.59 ± 0.001
AaltoCell™ C	1.57 ± 0.010
Vivapur 101	1.59 ± 0.013
A1	1.43 ± 0.003
B1	1.42 ± 0.003
C1	1.41 ± 0.006
D1	1.43 ± 0.001

In the measurement of densities, a reliable and repeatable measurement of bulk and tapped density could not be conducted for paracetamol, as the material was very cohesive and was not able to flow properly through the funnel without any further assistance. Thus, the bulk and tapped density collected for paracetamol was not presented in this work. Moreover, it was also challenging to determine bulk density for the MCC powders as they were cohesive and tended to adhere to the wall of the cylinder during pouring, making it difficult to read the bulk volume accurately. The measurement of the angle of repose of the MCC powders was not either performed successfully because the powders were very cohesive and was not able to flow through the funnel.

The bulk densities of the MCC powders were found to lie between 0.28-0.47 g/ml and 0.42-0.49 g/ml for the granulated formulations. The tapped densities for the MCC powders varied between 0.42-0.65 g/ml and for the granulated formulations the range was 0.52-0.57 g/ml. According to JRS Pharma and Handbook of pharmaceutical excipients (2009), the bulk density for Vivapur 101 is between 0.26 and 0.31 g/ml, so the bulk density of Vivapur 101 measured in this study agreed well with the literature. Different grades of MCC have a bulk density in the range of 0.13-0.50 g/ml. Among the four experimental MCCs in this study, AaltoCell™ C possessed the highest bulk density of 0.47 g/ml, whereas the bulk density values of AaltoCell™ B, AaltoCell™ C and Vivapur

101 did not differ greatly from each other, ranging from 0.28 g/ml to 0.31 g/ml. The granulated formulations containing AaltoCell^{TM} C also had the highest bulk density, which was 0.49 g/ml. The denser packing of AaltoCell^{TM} C might be due to the higher amount of large and regularly shaped particles, which had lower cohesiveness than the smaller and fibrous particles of AaltoCell^{TM} A and Vivapur 101 as discussed in the previous section (4.1 Particle size distribution and morphology). Other surface properties such as porosity and roughness also have an impact on the bulk density of the materials. Even though a low bulk density often hinders powder flow, previous studies have shown that a relatively high porosity and a low bulk density would be beneficial for manufacturing tablets with higher tensile strength (Badawy and Narang 2019; Johansson and Alderborn, 2001; Zhao et al, 2022).

The true density of the MCCs ranges between 1.512 g/ml to 1.668 g/ml according to the Handbook of pharmaceutical excipients (2009). Thus, the true density values determined for the MCC powders used in this study corresponded well with the literature. Sun (2005) developed a new method to measure the accurate true density of water-containing MCC and suggested that the true density of MCC should be in the range between 1.41-1.46 g/ml. According to the author, the true density of MCC obtained by helium pycnometry in prior research was not highly accurate, because water is released during the measurement which invalidates the underlying assumption of a constant number of molecules in the gaseous phase during the measurement (Sun and Grant 2004, Sun 2005). After high-shear wet granulation, the true densities of the formulations were almost similar, varying between 1.41 g/ml and 1.43 g/ml.

The flowability of AaltoCell^{TM} A was concluded to be very, very poor as proven by Carr's index and Hausner ratio. This observation is consistent with the low bulk density and numerous fine particles observed in the sample of AaltoCell^{TM} A. Besides the poor powder flow of MCC, paracetamol is known for its bad flowability and inadequate compressibility due to its crystal habits and poor plastic deformation (Beyer et al., 2001, Kaerger et al., 2004). Therefore, paracetamol blends can be granulated before compression to improve the flow and compaction properties (Rasenack and Müler 2002). As seen in Table 11, the flowability of the mixtures increased significantly after granulation. B1 and C1 had the best flowability among the four formulations and their flowability was classified as good, whereas the flow of A1 and V1 was fair according to

Carr's index and angle of repose values. The classifications based on Hausner ratio, Carr's index and angle of repose showed consistent results that the B1 and C1 formulations had good flowability and V1 and A1 had fair flowability. Gupta et al. (2020) suggested that a powder blend with a Hausner ratio under 1.43 would demonstrate robust tablet compression. Thus, in terms of flowability, all four formulations used in this study might be successfully compressed into tablets.

In the image-based analysis of powder flow, the flowability index value (FI%) was obtained as a function of the total percentage of the area of the analysis chamber covered by powder (Blanco et al, 2020). The higher the FI%, the better flowability a powder demonstrates. As seen in Figures 18 and 19, subtle differences in the flow and cohesive behaviour of the MCC powders and granulated formulations used in this study were distinguished. The comparison between the FI% obtained from the image-based analysis is compared with Carr's indexes in Figure 20.

In the study by Blanco et al. (2020), the results of flowability obtained from this method were consistent with Carr's index. Thus, based on the FI% values, MCC grades evaluated for flowability were classified in the right order with Carr's index values. However, in this study the FI% obtained from the image-based analysis of powders were contradictory to the powder flow classifications based on Carr's index, Hausner ratio and angle of repose. According to the FI% values, AaltoCell^{TM} B had the worst flowability among the four MCC powders used in this study and the flow of the granulated formulation containing AaltoCell^{TM} B (B1) was also poorer than the others. However, according to Carr's index, Hausner ratio and angle of repose, B1 had the best powder flow properties. The conflicting conclusions about the flowability tests could be explained by variability in the humidity conditions in the experiments. The image-based analysis was conducted only once in a relatively high humidity (40.7-43.2% RH), while the bulk and tapped density measurements were done at a RH of 22-25%. MCC is well-known for its high hygroscopicity due to the abundance of hydroxyl groups on cellulose chains and the relatively large surface-to-volume ratio of microfibrils (Ijima and Takeo 2000, Sun 2008). Sun (2008, 2016) observed that powder flow properties of MCC deteriorated continuously with rising RH and significant changes in flowability occurred when RH was above 32%. The flow results also suggested that AaltoCell^{TM} B might be more

moisture sensitive than the others. However, further investigation needs to be performed to understand the moisture sensitivity of AaltoCell™.

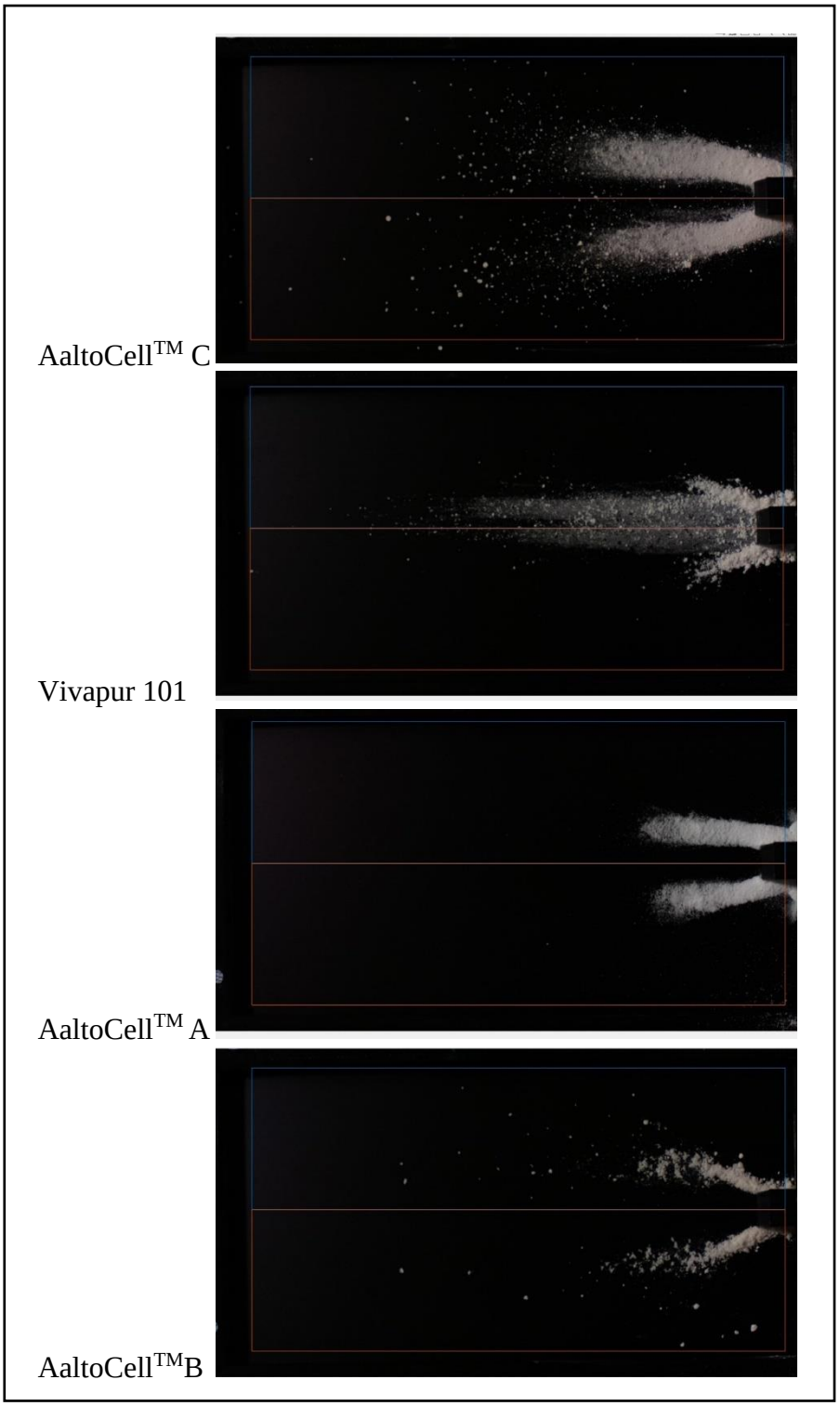


Figure 18. In-house optical powder flow characterization of the MCCs used in this study. Images are arranged in descending order of FI% from top to bottom.

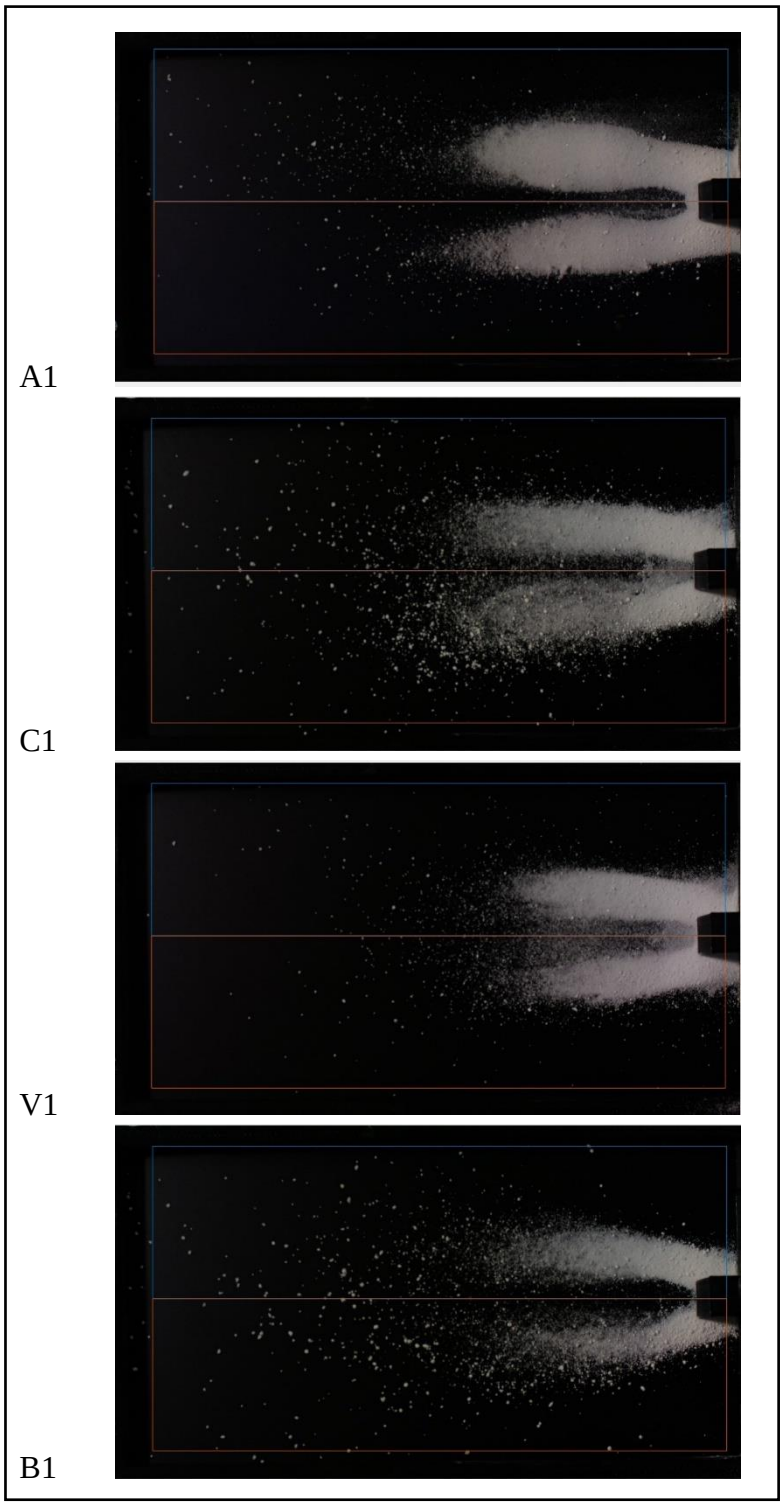


Figure 19. In-house optical powder flow characterization of the granulated formulations used in this study. Images are arranged in descending order of FI% from top to bottom.

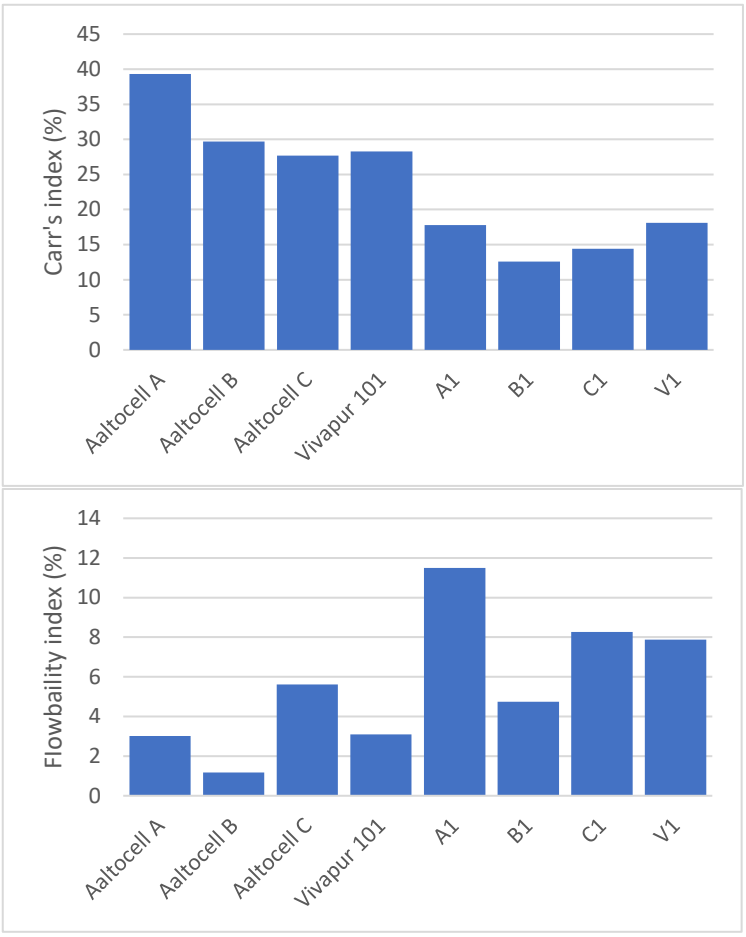


Figure 20. Comparison of the Carr's index and flowability index (FI%) obtained from the image-based analysis for the MCC powders and granulated formulations used in this study.

4.3 Physico-chemical properties of tablets

By visual inspection, the resulting tablets were rounded, white-coloured and scored on one side. The tablets compressed from V1 were smooth and shiny on the surface, whereas the tablets compressed from A1, B1 and C1 formulations were powdery and matt. No capping, laminating, or sticking to the punch faces occurred during tablet compression for any of the granulated formulations. The average, minimum and maximum compression force of the lower and the upper punch during the tableting process were also recorded (APPENDIX 2).

4.3.1 Vivpaur 101 tablets

Vivapur 101 was used as a reference to evaluate the properties of AaltoCell^{TM} for use in tablets. The results of Ph.Eur. tests for tablets compressed from the granulated formulation containing Vivapur 101 (V1) are presented in Table 13. The mean weight of V1 tablets was 3.2 % higher than the target weight (230 mg) and an increase in tablet weight during the compression was noticed when comparing tablets collected at the beginning (sample #1) and end (sample #2) of the tableting process. There was a statistically significant difference in tablet weight between sample #1 and sample #2 (p-value $3.17x10^{-8}$) (Table 14). On the other hand, the variation in tablet weight was low as the relative standard deviation was below 5%. V1 tablets had the highest weight loss among the four formulations in the friability test (APPENDIX 3), but they still fulfilled the criteria of European Pharmacopoeia for friability as none was cracked or broken after tumbling, and the weight loss was less than 1%. The V1 tablets did not only have acceptable friability, but they also achieved a very fast disintegration, as all tablets disintegrating within 1 min. Moreover, as seen in the dissolution profile (APPENDIX 4), V1 tablets showed a high dissolution rate of paracetamol, with 80% of paracetamol dissolved within 2 min. The fast disintegration of the tablets might enhance the dissolution of paracetamol, because a fast disintegration facilitates the break-up of the tablets into smaller fragments, enabling a faster release of API particles from the tablets (Markl and Zeitler 2017).

Content uniformity results showed that V1 tablets had a lower amount of paracetamol than expected, with the percentage of paracetamol varying from 46.4 – 48.4 % (label claim 50%). On the other hand, the relative standard deviation of the paracetamol content was 2.3 % and none deviated more than 15% from the average content. The acceptance value of the V1 formulation was 7.4, i.e., the lowest acceptance value in this study. Therefore, it can be concluded that the V1 tablets were uniform in drug content and the results were within the limits of content uniformity set by European Pharmacopoeia. The low variation in mass and drug content also indicated that the segregation of V1 during tableting was insignificant and the formulation had appropriate powder flow regardless of its small granule size.

Table 13. Properties and Ph.Eur. test results of tablets compressed from V1 formulation.

Property/test	Result	Comments
Weight (n=20)	237.4 ± 4.5 mg	The average weight of tablets was 3.2 % above the target weight (230 mg).
%RSD of weight	1.90%	Acceptable %RSD.
Diameter (n=20)	9.04 ± 0.004 mm	
Thickness (n=20)	2.98 ± 0.046 mm	
Breaking force	111.3 ± 8.3 N	1.2 % higher than the target breaking force
Tensile strength	2.63 ± 0.17 MPa	Acceptable tensile strength.
Friability	0.41 %	Complied with the Ph. Eur test (2.9.7).
Paracetamol content	112.1 ± 2.5 mg	The percentage of API in the tablets was between 46.4 – 48.4 %.
Acceptance value	7.4	Complied with the Ph. Eur test (2.9.40).
Number of tablets outside 85-115% of the average API content	0	Individual API content was between 96 – 102.8% of the average content. The preparation complied with the Ph. Eur test (2.9.6).
Disintegration test	All tablets (n=6) disintegrated within 1 minute	The tablets disintegrated very fast and passed the Ph. Eur test (2.9.1).
Dissolution test	The average amount of paracetamol released at 45 min was 91 %	Paracetamol was released from the tablets (n=6) almost completely after 45 min, Formulation complied with the dissolution requirements (Ph. Eur 2.9.3).

Table 14. Comparison between tablets collected during the beginning and the end of the tableting process of V1 formulation.

	Sample #1	Sample #2
Weight (n=10)	229.1 ± 2.4 mg *	238.3 ± 1.7 mg
Tensile strength (n=10)	2.58 ± 0.13 Mpa **	2.68 ± 0.21 Mpa

* p-value 3.17×10^{-8} ** p-value 0.19

4.3.2 AaltoCell^{TM} A tablets

The results of Ph. Eur. tests for tablets compressed from AaltoCell^{TM} A containing granulated formulation (A1) are presented in Table 15.

The mean weight of tablets (n=20) compressed from A1 was 228 mg, which was close to the target weight (230 mg). The individual tablet weights were within ± 2.4 % of the average value, and none differed more than 7.5 %. Therefore, the tablets met the requirements for uniformity of mass, as well as complied with the other Ph.Eur. tests conducted in this study. The low relative standard deviation value (%RSD) of weight variation (RSD 1.18 %) indicated a narrow tablet weight variation and homogeneous die filling, which might be facilitated by adequate powder flow and suitable particle size. Content uniformity results showed that paracetamol content in the tablets exceeded the label claim (50%). Paracetamol content varied from 52.7 to 54.5 %. Despite this, the tablets were uniform in content as none was outside the limit of 85 – 115% and the acceptance value was below 15.

AaltoCell^{TM} A tablets had lower friability (0.31%) than Vivapur 101 tablets and fulfilled the requirement of European Pharmacopoeia for friability. Moreover, AaltoCell^{TM} A tablets had fast disintegration – all of six tablets disintegrated completely within a minute.

Table 15. Properties and Ph.Eur. test results of tablets compressed from A1 formulation.

Property/test	Result	Comments
Weight (n=20)	228.0 ± 2.7 mg	The average weight of tablets was 0.9% below the target weight.
%RSD of weight	1.18 %	Acceptable %RSD. The lowest %RSD of weight among four formulations.
Diameter (n=20)	9.04 ± 0.007 mm	
Thickness (n=20)	2.96 ± 0.035	
Breaking force	117.3 ± 9.17 N	6.4% higher than the target breaking force.
Tensile strength	2.80 ± 0.20 MPa	Acceptable tensile strength.
Friability	0.31 %	Complied with the Ph. Eur test (2.9.7)
Paracetamol content	122.1 ± 2.3 mg	The percentage of API in the tablets was between 52.7-54.5 %.
Acceptance value	12.5	Complied with the Ph. Eur test (2.9.40).
Number of tablets outside 85-115% of the average API content	0	Individual API content was between 96.1 – 101.8% of the average content. The preparation complied with the Ph. Eur test (2.9.6).
Disintegration test	All the tablets tested (n=6) disintegrated within a minute	The tablets had rapid disintegration and the passed the Ph. Eur test (2.9.1).
Dissolution test	Average amount of paracetamol released at 45 min was 97.9 %	Paracetamol released from the tablets (n=6) almost completely after 45 min, Formulation complied with the dissolution requirements (Ph.Eur 2.9.3).

Usually, a tensile strength greater than 2.0 MPa is recommended because tablets with a tensile strength of 2.0 MPa can withstand stress from further handling until end-use by patients (Pitt and Heasley 2013, Sun et al. 2009). Thus, the tensile strength value of tablets prepared from the A1 formulation was acceptable. There was a statistically significant difference (p-value $1.23x10^{-5}$) in the mean weight of the tablets collected at the beginning (sample #3) and the end (sample #4) of the tableting process (Table 16). However, there was no statistical significance (p-value 0.066) in the tablet tensile strength between sample #3 and sample #4

Tablet 16. Comparison between tablets collected during the beginning and the end of the tableting process of A1 formulation.

	Sample #3	Sample #4
Weight (n=10)	223.0 ± 3.1 mg *	230.6 ± 4.5 mg
Tensile strength (n=10)	2.72 ± 0.16 MPa**	2.89 ± 0.20 MPa

* p-value = $1.23x10^{-5}$', ** p-value = 0.066

4.3.3 AaltoCell^{TM} B tablets

The tablets prepared from the granulated formulation containing AaltoCell^{TM} B (B1) fulfilled the requirements of European Pharmacopoeia in terms of mass uniformity, content uniformity, friability, disintegration, and dissolution (Table 17). The mean weight of the tablets (229.1 ± 4.2 mg) was close to the target weight (230 mg), and none of the tablets had an individual weight that deviated more than 7.5% from the average weight. The maximum individual weight variation from the average value was 2.5% for formulation B1 compared to 2.3% for formulation A1 and 3.2% for formulation V1. The relative standard deviation of the weights of B1 (RSD 1.84%) and V1 (RSD 1.90%) was higher than the value of formulation A1 (RSD 1.17%). Thus, based on the results of mass uniformity and RSD values, the tablets compressed from the A1 formulation had lower mass deviation compared to B1 tablets. The difference might be caused by variations in powder flow and die filling during the tableting process.

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Table 17. Properties and Ph.Eur. test results of tablets compressed from B1 formulation.

Property/test	Results	Comments
Weight (n=20)	229.1 ± 4.2 mg	The average weight of tablets was only 0.4% below the target weight.
%RSD of weight	1.84%	Acceptable % RSD.
Diameter (n=20)	9.04 ± 0.004 mm	
Thickness (n=20)	2.97 ± 0.04 mm	
Breaking force	115.8 ± 11.1 N	4.5% higher than the desired breaking force.
Tensile strength	2.74 ± 0.23 MPa	Adequate tensile strength that ensures the mechanical durability of tablets.
Friability	0.31 %	Complied with the Ph. Eur test (2.9.7).
Paracetamol content (n=10)	124.1 ± 2.6 mg	The percentage of API in the tablets was between 52.9-56.9 %.
Acceptance value	12.7	Complied with the Ph. Eur test (2.9.40).
Number of tablets outside the 85-115% limit of the average API content	None was outside the limit of 85-115 %.	Individual API content was between 96.3–102.1% of the average content. The preparation complied with the Ph. Eur test (2.9.6).
Disintegration test (n=6)	All tablets disintegrated completely within 8.5 minutes	The tablets fulfilled the requirements for disintegration (Ph. Eur 2.9.1).
Dissolution test (n=6)	The average amount of paracetamol released at 45 min was 98 %.	Complete dissolution of tablets was achieved after 45 min. Formulation complied with the Ph. Eur dissolution test (2.9.3).

As seen in Table 17, the B1 tablets had significantly longer disintegration time in comparison with the A1 and V1 tablets. All B1 tablets disintegrated within 8.5 min, but when visually inspecting the tablets during the disintegration test, it was noticed that two out of six tablets had fast disintegration, within 2 minutes, while the rest four tablets had palpably hard cores, which disintegrated very slowly. Regardless of the longer disintegration time, formulation B1 met the disintegration criteria as there was no palpable core present after 8.5 minutes

When comparing the tablets collected during the beginning (sample #5) and the end (sample #6) of tablet compression, it was noticed that the average tensile strength of sample #6 was 14.5% higher than the average tensile strength of sample #5 (Table 18). This might be caused by the increasing compression force during the tableting process (APPENDIX 2). There was also a statistically significant relationship between the two samples in tablet weight and tensile strength.

Table 18. Comparison between tablets collected during the beginning and the end of the tableting process of B1 formulation.

	Sample #5 (n=10)	Sample #6 (n=10)
Weight	228.2 ± 4.5 mg*	231.9 ± 2.2 mg
Tensile strength	2.55 ± 0.15 MPa**	2.92 ± 0.12 MPa

* p-value = 1.97×10^{-6}, ** p-value = 7.17×10^{-6}

4.3.4 AaltoCell^{TM} C tablets

The properties and results of tablet analyses for tablets compressed from the granulated formulation containing AaltoCell^{TM} C (C1) are listed in Table 19. The average weight of the tablets was 2.3% above the target weight (230 mg), but it could be reduced by adjusting the die filling. In this study, the powders flowed into the dies through a gravity filling mechanism, and the fill depth was controlled manually. Thus, the filling system might not be sufficient to control the tablet weight.

Table 19. Properties and Ph.Eur. test results of tablets compressed from C1 formulation.

Property/test	Results	Comments
Weight (n=20)	235.3 ± 3.1 mg	The average weight of tablets was 2.3% above the target weight.
%RSD of weight	1.31%	Acceptable %RSD.
Diameter (n=20)	9.04 ± 0.008 mm	Tablets had similar dimensions as V1, A1 and B1, even though the average weight was higher.
Thickness (n=20)	2.98 ± 0.05 mm	
Breaking force	111.3 ± 8.3 N	1.2 % higher than the desired breaking force.
Tensile strength	2.63 ± 0.18 MPa	Slightly lower than the tensile strength of A1 and B1 tablets but still met the criteria for friability.
Friability	0.30 %	Complied with the Ph. Eur friability test (Ph. Eur 2.9.7).
Paracetamol content (n=10)	124.9 ± 3.0 mg	The percentage of API in the tablets was between 52.6-54.8 % and %RSD of content was the highest (2.43 %).
Acceptance value	13.4	Complied with the Ph. Eur test (2.9.40).
Number of tablets outside the 85-115% limit of the average API content	None was outside the limit of 85-115 %	Individual API content was between 96.3–102.1% of the average content. The preparation complied with the Ph. Eur test (2.9.6).
Disintegration test (n=6)	All tablets disintegrated completely within 4 min	The tablets fulfilled the requirements for disintegration (Ph. Eur 2.9.1).
Dissolution test (n=6)	Average amount of paracetamol released at 45 min was 93.5 %	Formulation complied with the dissolution requirements of Ph. Eur (2.9.3).

The C1 tablets had lower tensile strength than A1 and B1 tablets, even though a higher compression force was applied for the C1 formulation (APPENDIX 2). However, differences in the tensile strength of tablets did not likely pose an impact on the results of friability because C1 tablets had similar maximum weight loss (0.30 %) in the friability test as A1 and B1 tablets. All C1 tablets disintegrated completely within 4 min and had rapid dissolution with 87% paracetamol dissolved within 3 min (APPENDIX 4). As shown in Table 19, C1 also complied with all the Ph.Eur. quality tests conducted in this study

When comparing the C1 tablets collected from the initial (sample #7) and the final stage (sample #8) of the tableting process, it was found that C1 showed the same trend as other formulations that the tablet weight and tensile strength increased towards the end of the tablet compression (Table 20). There was a statistically significant difference (p-value $3.23x10^{-8}$) in the mean weight of sample #7 and sample #8, but no statistical significance was observed in the tablet tensile strength (p-value = 0.195).

Table 20. Comparison between tablets collected during the beginning and the end of the tableting process of C1 formulation

	Sample #7 (n=10)	Sample #8 (n=10)
Weight	229.2 ± 2.4 mg*	238.3 ± 1.7 mg
Tensile strength	2.58 ± 0.13 MPa**	2.68 ± 0.21 MPa

* p-value = $3.23x10^{-8}$, ** p-value = 0.195

4.3.5 Discussion of tablet properties

All formulations in the present study showed low variations in tablet weight, having standard deviation values between 1.18-190%. Surprisingly, A1 tablets had the lowest weight variation. The A1 granulated formulation had the smallest particle size (D_{50} = 85 μm), poorer flowability than B1 and C1 according to Carr's index and an excess amount of fine particles observed in the PLM analysis. Thus, the flow of the granulated formulation A1 from the feed shoe of the tableting machine was predicted to occur less smoothly than for the granulated formulations of C1 and B1, thus influencing mass and drug content uniformity. However, the results of mass and content uniformity of tablets

showed that in this study, the smaller particle size of the granulated formulation A1 did not affect its flowability as the A1 tablets were uniform in mass and drug content.

The amount of paracetamol in the tablets deviated slightly from the target content of 50%, and all four granulated formulations used in this study showed a similar trend that their tablet weight and tensile strength increased toward the end of the tableting process. This can be explained by an increased compression force during tablet compression, which might cause increased tablet weights and tensile strength. The tableting process parameters, including die filling and compression force, were adjusted manually to obtain the desired tablet weight and breaking force. Hence, the compression force varied for each formulation, resulting in different tablet weights and paracetamol contents between the formulations. Thus, the API content in the tablets deviated slightly from the target content (50% of paracetamol). To address these issues, the rotary tablet press should be calibrated before use and after each formulation. In addition, a force feeder can be utilized instead of a gravity feeder in rotary tablet presses for more efficient die filling.

When evaluating the tablet tensile strength, there was no correlation observed between the tensile strengths and the compression forces. Generally, the tensile strength of tablets is influenced by the formulation as well as the processing parameters, such as the compression force and compression speed. During compression, MCC undergoes plastic deformation, which is a stress-and time-dependent behaviour (Wu et al. 2001b). Hence, compression force and speed have a significant impact on the tablet strength, where an increase in compression force results in stronger tablets, while an increase in compression speed leads to a reduction in the tensile strength of tablets. In this study, the compression speed remained the same for all formulations. The tensile strength results indicated that the A1 formulation produced stronger tablets with a lower force compared to the C1 and B1 formulations (APPENDIX 2). This might be caused by a higher granule porosity, because in dry and wet granulation processes, granules of higher porosity have been reported to generate tablets with higher tensile strength (Nordström and Alderborn, 2015, Zuurman et al., 1994). Another factor that could affect the tensile strength was the particle shape. A more irregular shape may enhance the mechanical interlocking of particles during compression, resulting in stronger tablets (Nordström and Alderborn, 2015). It has also been reported that granules having smaller size were able to generate tablets with higher tensile strength due to larger surface-to-volume ratios, leading to the formation of

stronger bonds between smaller granules than with larger granules (Tan et al., 2011). As discussed previously (section 4.1 Particle size and morphology), the A1 formulation had a more irregular shape and smaller granule size. This could explain why the tablets compressed from the A1 formulation had higher tensile strength. However, one should note that the tensile strength results are mean values and possible errors in measuring tablet dimensions and breaking force can affect the tensile strength results. Moreover, an increase in relative humidity has been reported to reduce the tensile strength of MCC compacts (Williams et al., 1997). In the present study, the tablets were stored only in zip bags under uncontrolled relative humidity and room temperature. Thus, storage condition variables could also influence the tensile strength results.

All tablets prepared in this study had a disintegration time between 1-8.5 min (APPENDIX 3). A1 and V1 tablets had the shortest disintegration time within 1 min, whereas B1 tablets had a considerably longer disintegration time of 8.5 min. In general, tablets with higher tensile strength have stronger interparticle bonding, which hinders water penetration into tablets. However, A1 had fast disintegration even though it had the highest tablet tensile strength (2.80 MPa) and smallest granule size. This observation was contradictory with earlier studies where MCC grades with small particle size had a longer disintegration time, because smaller particles packed more densely and had a larger bonding area with relatively small interparticular pores (Lahdenpää et al., 1997). The disintegration is also affected by the porosity of the final tablets (Mark and Zeitler 2017, Yassin et al., 2015). A more porous structure allows a faster penetration of water into tablets, thus enhancing the subsequent swelling process. In this study, the tablet porosity was not investigated. Analysing the porosity of the tablets may give an explanation for the differences in disintegration ability between the different tablets. All in all, all the tablets in this study fulfilled the requirement of the European Pharmacopoeia for disintegration and exhibited a rapid drug release.

One limitation of this study was that the tablets were produced using a laboratory-scale rotary tablet press, which was not able to manufacture larger tablets containing 500 mg of paracetamol. Therefore, it was not possible to perform a comparison between the formulations used in this study with a commercial product of paracetamol. Another limitation was that, as discussed above, the formulations were not stored in controlled humidity and their moisture contents were not determined before the tableting. MCC is

known to have high hygroscopicity and hence, variations in moisture content will have an impact on the compaction behaviour of MCC mixtures and the tablet properties, such as tensile strength. In further studies, it would be beneficial to investigate the effect of relative humidity on the compactability of AaltoCell™.

5 CONCLUSIONS

In this study, three grades of AaltoCell™ MCC granulated with high-shear wet granulation were successfully utilized for the preparation of paracetamol tablets with a 50% (w/w) drug load. According to the results of PLM analysis and flowability, the AaltoCell™ C powder had better flow properties than Vivapur 101, AaltoCell™ A and AaltoCell™ B due to its larger particle sizes and more regular shape. Moreover, AaltoCell™ C had a bulk density of 0.47 g/ml, which was the highest bulk density among the four MCC powders used in this study. Based on Carr's index and Hausner ratio, the flowability of AaltoCell™ A was classified to be very, very poor. The poor powder flow properties of AaltoCell™ A could be explained by its smaller and rod-shaped particles. After the high-shear wet granulation, the flowability and particle size of the formulations were significantly improved. The AaltoCell™ B formulation had the largest granule size and the best flow properties according to Carr's index, Hausner ratio and angle of repose. However, this result was conflicting with the flowability index obtained by the image-based analysis. According to the flowability index, AaltoCell™ B formulation had the worst flow among the four granulated formulations. One explanation for this could be that the results of Carr's index and Hausner's ratio are dependent on the experimental conditions, such as relative humidity, temperature, and the number of times the sample is tapped (Adejar 2021). Especially, the moisture content of the powder has a significant impact on the flowability for hygroscopic materials such as MCC. In this study, the image-based analysis was conducted in considerably higher relative humidity than the experiments for determining the Carr's index, Hausner ratio and angle of repose. Thus, variations in the powder flow properties between the methods used in this study could originate from the difference in relative humidity conditions during the measurements. As discussed earlier, AaltoCell™ B seemed to be slightly more sensitive to moisture than

Vivapur 101 and other AaltoCell™ grades. However, no definitive conclusion about the moisture sensitivity of AaltoCell™ can be drawn based on the experiments performed in this study. In further studies, the effect of relative humidity on the powder properties of AaltoCell™, and its effect on the tableting properties should be further studied or taken into consideration.

According to the results of the tablet analyses in this work, the tablets compressed from the formulations containing AaltoCell™ MCC complied with the requirements of Ph.Eur. in terms of friability, disintegration, dissolution, uniformity of mass and content. The quality of AaltoCell™ tablets was comparable with Vivapur 101 tablets. AaltoCell™ tablets were uniform in mass and content, having acceptable weight and API content variations. This indicated that the AaltoCell™ formulations had good powder flow properties and homogeneous die filling ability during tablet compression. AaltoCell™ tablets achieved a higher tensile strength than 2MPa and had a good mechanical durability, which is corroborated by the weight loss in the friability test that was only 0.30-0.31%, and which was lower than the weight loss of Vivapur 101 tablets (0.41%). Among the four granulated formulations, AaltoCell™ A tablets had the lowest weight variation. This was surprising because the AaltoCell™ A formulation had the smallest granule size. Hence, its powder flow during the compression was expected to be poor, which could cause nonhomogeneous die filling during tableting. In addition, AaltoCell™ A tablets had the highest tensile strength, but still disintegrated rapidly within 1 minute. AaltoCell™ A and AaltoCell™ B tablets also had a faster dissolution than Vivapur 101, having more than 80% of paracetamol released within 1 minute.

In conclusion, the experimental MCC grades of AaltoCell™ are promising new filling materials for tablets compressed from high-shear wet granulated formulations. However, it should be kept in mind that, in this study, the methods used to characterize the flowability and morphology of the MCCs do not reflect all aspects of the powder properties. In the future, a better understanding of particle shape, porosity, hygroscopicity, and surface roughness of AaltoCell™ would be necessary to better understand the behaviour and interactions of AaltoCell™ for optimizing tableting purposes.

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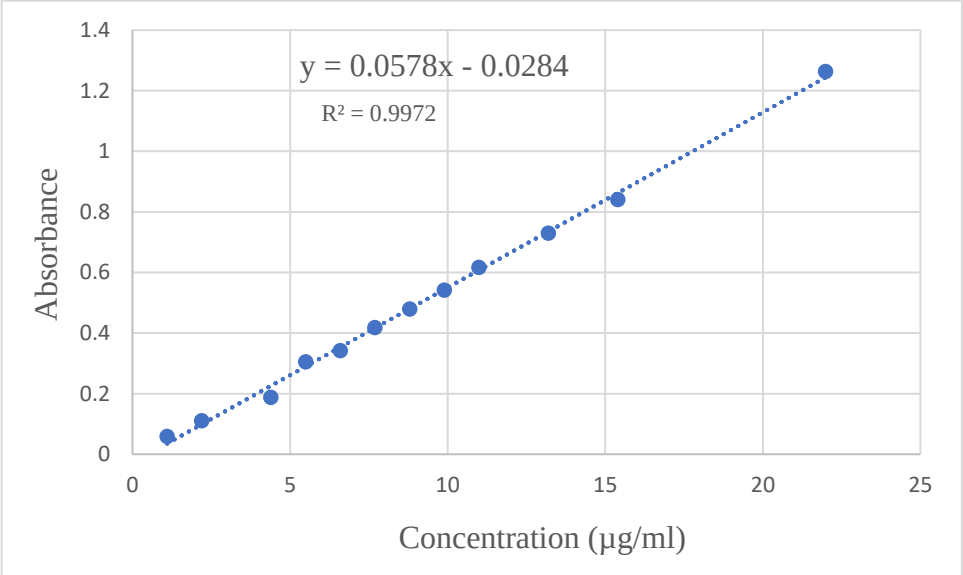
APPENDICES

APPENDIX 1

The standard curve of paracetamol for the dissolution and content uniformity tests.



APPENDIX 2

Compression forces recorded during tablet compression.

	Lower punch			Upper punch		
Sample	Avg. (N)	Min. (N)	Max. (N)	Avg. (N)	Min. (N)	Max. (N)
A1	9384	8086	10354	10412	9224	11124
B1	10379	8602	11598	11253	9744	12560
C1	13369	11132	14927	14009	12092	15160
V1	8886	7244	10629	9903	8536	11132

APPENDIX 3

Summary of the properties of the formulations in this study

RSD = relative standard deviation

The results of particle size, bulk density, tablet weight, tensile strength, paracetamol content and % paracetamol released are mean values.

Formulation	D_{50} value (µm)	Bulk density (g/ml)	Carr' s index	Hausner ratio	Angle of repose (^{O})	Fowability index %	Tablet weight (mg)	RSD %	Tensile strength (MPa)	RSD%	Paracetamol content (mg)	RSD%	Acceptance Value	Friability %	Disintegration time (min)	% paracetamol released at 45 min
A1	85	0.42	17.8	1.21	38.0	11.5	228.0	1.17	2.80	7.03	122.1	1.85	12.5	0.31	1	98.0
B1	318	0.48	12.6	1.14	33.0	4.74	229.1	1.84	2.74	8.43	124.1	2.09	13.4	0.31	8.5	98.5
C1	161	0.49	14.4	1.17	33.9	8.27	235.3	1.30	2.63	6.67	124.9	2.43	12.7	0.30	4	93.5
V1	90	0.45	18.1	1.22	37.5	7.87	237.4	1.90	2.63	6.69	112.1	2.26	7.4	0.41	1	91.0

APPENDIX 4

The average release profile (n=6) of paracetamol from different formulations prepared in this study.